REGISTER
for online access to
the full text of the BJA at:
http://bja.oupjournals.org

THE POWER TO
RISE
ABOVE
PAIN
5mg
now available
IN
MALIGNANCY
AND
POST-OPERATIVE
PATIENTS
12-HOURLY
▼ OxyContin®
Prolonged release oxycodone hydrochloride table
www.napp.co.uk/pain pass d: 120012
A REAL ADVANCE IN OPIOID ANALGESIA

P25803

PRESCRIBING INFORMATION OxyContin®▼ 5 mg, 10 mg, 20 mg, 40 mg, 80 mg tablets United Kingdom **Presentation** Film-coated, prolonged release tablets containing oxycodone hydrochloride, marked OC on one side and the strength of oxycodone hydrochloride on the other. The 5 mg tablets are blue and contain 5 mg of oxycodone hydrochloride. The 10 mg tablets are white and contain 10 mg of oxycodone hydrochloride. The 20 mg tablets are pink and contain 20 mg of oxycodone hydrochloride. The 40 mg tablets are yellow and contain 40 mg of oxycodone hydrochloride. The 80 mg tablets are green and contain 80 mg of oxycodone hydrochloride. **Indications** For the treatment of moderate to severe pain in patients with cancer and post-operative pain. **Dosage and administration** OxyContin tablets must be swallowed whole, and not chewed. *Elderly and adults over 18 years:* OxyContin tablets should be taken at 12-hourly intervals. The dosage is dependent on the severity of the pain, and the patient's previous history of analgesic requirements. The usual starting dose for opioid naive patients or patients presenting with severe pain uncontrolled by weaker opioids is 10 mg, 12-hourly. Some patients may benefit from a starting dose of 5 mg especially those with renal or hepatic impairment. If higher doses are necessary, increases should be made, where possible in 25% – 50% increments. Patients transferring from morphine should have the daily dose based on the following ratio: 10 mg oral oxycodone is equivalent to 20 mg oral morphine. For most patients the maximum dose of OxyContin tablets is 200 mg, 12-hourly. However, a few patients may require higher doses. Doses in excess of 1000 mg have been reported. *Children under 18 years:* Not recommended. **Contra-indications** Respiratory depression, head injury, paralytic ileus, acute abdomen, delayed gastric emptying, chronic obstructive airways disease, chronic bronchial asthma, hypercarbia, known oxycodone sensitivity, moderate to severe hepatic impairment, severe renal impairment, chronic constipation, concurrent administration of monoamine oxidase inhibitors or within 2 weeks of discontinuation of their use. Not recommended for pre-operative use or for the first 24 hours post-operatively. Pregnancy. **Precautions and warnings** A reduction in dosage may be advisable in hypothyroidism. Use with caution in opioid dependent patients and in patients with raised intracranial pressure, hypotension, hypovolaemia, toxic psychosis, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, prostatic hypertrophy, adrenocortical insufficiency, acute alcoholism, delirium tremens, chronic renal and hepatic disease, severe pulmonary disease and debilitated patients. OxyContin tablets should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, OxyContin tablets should be discontinued immediately. Patients who are to undergo cordotomy or other pain relieving surgical procedures should not receive OxyContin tablets for 24 hours before surgery. If further treatment with OxyContin tablets is then indicated the dosage should be adjusted to the new post-operative requirement. OxyContin 80 mg should not be used in patients not previously exposed to opioids. OxyContin tablets should be used with caution following abdominal surgery, as opioids are known to impair intestinal motility and should not be used until the physician is assured of normal bowel function. OxyContin tablets must be swallowed whole and not broken, chewed or crushed. **Pregnancy and lactation** Not recommended. Oxycodone is secreted in breast milk and may cause respiratory depression in the newborn. OxyContin tablets should, therefore, not be used in breast-feeding mothers. **Side-effects** Adverse drug reactions are typical of full opioid agonists. Tolerance and dependence occur. The most common adverse reactions seen during therapy are constipa nausea, vomiting, dry mouth, anore dyspepsia, abdominal pain, diarrho headache, confusion, asthenia, faintne dizziness, sedation, anxiety, abnormal drea nervousness, insomnia, thought abnormalit drowsiness, twitching, orthostatic hypotens bronchospasm, dyspnoea, decreased co reflex, rash, pruritus, sweating, chills. **Le category** CD (Sch2) POM **Package quanti and price** 5 mg – £10.72 (28 tablets) 10 m £21.43 (56 tablets) 20 mg – £42.86 (56 table 740 mg – £85.73 (56 tablets) 80 mg – £171 (56 tablets) **Marketing Authorisation numb** PL 16950/0097-0100, 0123 **Market Authorisation holder** Napp Pharmaceutic Limited, Cambridge Science Park, Milton R Cambridge CB4 0GW UK. Tel: 01223 424 Member of the Napp Pharmaceut Group. Further information is available f Napp Pharmaceuticals Limited. **Date preparation** May 2002. ®OxyContin and NAPP device are Registered Trade Mar ©Napp Pharmaceuticals Limited 2 European Patent (UK) 0 253 104 Europ Patent (UK) 0 576 643. European Pat Application No. 96102992.3. **Date of prepara** May 2002.

A leader
NAPP
in pain control

BJA
International Journal of Anaesthesia
Volume 89 Number 3 September 2002

EDITORIALS

369 I. Confidential enquiries into maternal deaths, 1997–1999
G. M. Cooper, G. Lewis and J. Neilson

373 II. Pressure support ventilation and the critically ill patient with muscle weakness
J. W. H. Watt

CLINICAL INVESTIGATIONS

376 Impaired explicit memory after recovery from propofol/sufentanil anaesthesia is related to changes in the midlatency auditory evoked response
I. Rundshagen, K. Schnabel and J. Schulte am Esch

382 Effect of propofol anaesthesia on the event-related potential mismatch negativity and the auditory-evoked potential N1
T. P. Simpson, A. R. Manara, N. M. Kane, R. L. Barton, C. A. Rowlands and S. R. Butler

389 Prediction of the haemodynamic response to tracheal intubation: comparison of laser-Doppler skin vasomotor reflex and pulse wave reflex
M. Luginbühl, F. Reichlin, G. H. Sigurdsson, A. M. Zbinden and S. Petersen-Felix

398 Incidence and risk calculation of inotropic support in patients undergoing cardiac surgery with cardiopulmonary bypass using an automated anaesthesia record-keeping system
M. Müller, A. Junger, M. Bräu, M. M. Kwapisz, E. Schindler, H. Akintürk, M. Benson and G. Hempelmann

405 Delays in defibrillation: influence of different monitoring techniques
G. D. Perkins, C. Roberts and F. Gao

409 Effectiveness of acute postoperative pain management: I. Evidence from published data
S. J. Dolin, J. N. Cashman and J. M. Bland

424 Comparison of morphine alone with morphine plus clonidine for postoperative patient-controlled analgesia
S. A. Jeffs, J. E. Hall and S. Morris

428 Contribution of midazolam and its 1-hydroxy metabolite to preoperative sedation in children: a pharmacokinetic-pharmacodynamic analysis
T. N. Johnson, A. Rostami-Hodjegan, J. M. Goddard, M. S. Tanner and G. T. Tucker

438 Pharmacokinetics of 0.75% ropivacaine and 0.5% bupivacaine after ilioinguinal–iliohypogastric nerve block in children
T. I. Ala-Kokko, J. Karinen, E. Räihä, K. Kiviluoma and S. Alahuhta

442 Evaluation of S1 motor block to determine a safe, reliable test dose for epidural analgesia
Z. Daoud, R. E. Collis, B. Ateleanu and W. W. Mapleson

446 Effect of thoracic epidural anaesthesia on colonic blood flow
T. H. Gould, K. Grace, G. Thorne and M. Thomas

452 Comparison of intrathecal fentanyl and diamorphine in addition to bupivacaine for Caesarean section under spinal anaesthesia
C. M. Cowan, J. B. Kendall, P. M. Barclay and R. G. Wilkes

459 Patient-controlled epidural analgesia *versus* continuous infusion for labour analgesia: a meta-analysis
M. van der Vyver, S. Halpern and G. Joseph

466 Epidural analgesia and backache: a randomized controlled comparison with intramuscular meperidine for analgesia during labour
B. A. Loughnan, F. Carli, M. Romney, C. J. Doré and H. Gordon

473 Management of post-strabismus nausea and vomiting in children using ondansetron: a value-based comparison of outcomes
B. Sennaraj, D. Shende, S. Sadhasivam, S. Ilavajady and D. Jagan

LABORATORY INVESTIGATIONS

479 Effects of halothane and isoflurane on the contraction, relaxation and energetics of rat diaphragmatic muscle
B. Bouhemad, O. Langeron, G. Orliaguet, P. Coriat and B. Riou

486 Pharmacological preconditioning: comparison of desflurane, sevoflurane, isoflurane and halothane in rabbit myocardium
V. Piriou, P. Chiari, F. Lhuillier, O. Bastien, J. Loufoua, O. Raisky, J. S. David, M. Ovize and J.-J. Lehot

492 Role of propofol and its solvent, intralipid, in nitric oxide-induced peripheral vasodilatation in dogs
M.-F. Doursout, P. M. Joseph, Y. Y. Liang, C. J. Hartley and J. E. Chelly

REVIEW ARTICLE

499 Maternal deaths from anaesthesia. An extract from *Why Mothers Die 1997–1999*, the Confidential Enquiries into Maternal Deaths in the United Kingdom
T. A. Thomas and G. M. Cooper, on behalf of the Editorial Board of the Confidential Enquiries into Maternal Deaths in the United Kingdom

SHORT COMMUNICATION

509 Effect of a single dose of esmolol on the bispectral index scale (BIS) during propofol/fentanyl anaesthesia
H. Berkenstadt, R. Loebstein, I. Faibishenko, H. Halkin, I. Keidan and A. Perel

CASE REPORTS

512 Flow-by induced hypoventilation in high spinal cord lesions—report of two cases
S. Kannan, N. Sherwood and A. Armfield

514 Posterior spinal ligament rupture associated with laryngeal mask insertion in a patient with undisclosed unstable cervical spine
C. J. Edge, N. Hyman, V. Addy, P. Anslow, C. Kearns, R. Stacey and C. Waldmann

517 Complete airway obstruction in a ventilated patient after oesophageal dilatation
S. Francis, W. C. Russell and J. P. Thompson

519 Coronary artery spasm and non-Q-wave myocardial infarction following intravenous ephedrine in two healthy women under spinal anaesthesia
A. Wahl, F. R. Eberli, D. A. Thomson and M. Luginbühl

524 CORRESPONDENCE

530 BOOK REVIEWS

PHILIPS
Let's make things b

Is that an x-ray image on the monitor?

Yes. See for yourself.
Association of Anaesthetists
Annual Scientific Meeting, Bournemouth
Sept. 19-20, 2002

CUK-H05608-54-P25803

B.J.A

British Journal of Anaesthesia

Editorial Board

Editor-in-Chief

JENNIFER M. HUNTER, Professor of Anaesthesia, *University of Liverpool*

Editors

G. B. DRUMMOND, Senior Lecturer in Anaesthesia, *Royal Infirmary, Edinburgh*
P. M. HOPKINS, Professor of Anaesthesia, *University of Leeds*
D. G. LAMBERT, Reader in Anaesthetic Pharmacology, *University of Leicester*
D. J. ROWBOTHAM, Professor of Anaesthesia and Pain Management, *University of Leicester*

Board Members

F. BONNET, Professor of Anaesthesia, *Assistance Publique Hopitaux de Paris*
H. F. GALLEY, Senior Lecturer in Anaesthesia and Intensive Care, *University of Aberdeen*
G. M. HALL, Professor of Anaesthesia, *University of London*
S. J. HOWELL, Senior Lecturer in Anaesthesia, *University of Leeds*
P. HUTTON, President, *Royal College of Anaesthetists*
D. M. JUSTINS, Vice-president, *Royal College of Anaesthetists*
P. A. LONNQVIST, Associate Professor of Paediatric Anaesthesia and Intensive Care, *Lingrens Children's Hospital, Stockholm, Sweden*
R. D. MILLER, Professor of Anesthesia, *University of California, San Francisco*
I. POWER, Professor of Anaesthesia, Critical Care and Pain Medicine, *University of Edinburgh*
H.-J. PRIEBE, Professor of Anaesthesia, *University of Freiburg, Germany*
C. S. REILLY (Treasurer), Professor of Anaesthesia, *University of Sheffield*
J. SEAR, Clinical Reader in Anaesthesia, *University of Oxford*
P. J. SIMPSON, Vice-president, *Royal College of Anaesthetists*
G. SMITH (Chairman), Professor of Anaesthesia, *University of Leicester*
J. R. SNEYD, Professor of Anaesthesia, *University of Plymouth*
D. R. SPAHN, Professor of Anaesthesia, *University Hospital, Lausanne, Switzerland*
N. R. WEBSTER (Secretary), Professor of Anaesthesia, *University of Aberdeen*
J. A. W. WILDSMITH, Professor of Anaesthesia, *Ninewells Hospital and Medical School, Dundee*
J. D. YOUNG, Reader in Anaesthesia, *Radcliffe Infirmary, Oxford*

International Board Members

F. CARLI, Wesley Bourne Professor and Chairman, Department of Anesthesia, *McGill University, Montreal, Canada*
K. HIROTA, Department of Anesthesiology, *University of Hirosaki, Japan*

Assistant Editors

R. S. JONES, Professor of Veterinary Anaesthesia, *University of Liverpool*
B. V. S. MURTHY, Consultant Anaesthetist, *Royal Liverpool University Hospital*

Production Staff

E. GOODING, Senior Production Editor, *Oxford University Press*
H. J. LAMB, Production Editor, *Oxford University Press*

University College
LIBRARY

Please visit the Journals's World Wide Web site at http://bja.oupjournals.org

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

General Information

Subscriptions

All Fellows of the College, world-wide, should notify changes of address directly to the Royal College of Anaesthetists.

An annual subscription to *BJA* comprises 12 issues (two volumes of 6 issues), with Author and Subject Indexes. Subscriptions are entered on a calendar year basis only. Please add local sales tax to the prices quoted. Prices include postage by surface mail, or for subscribers in the USA and Canada by Airfreight, or in Japan, Australia, New Zealand, and India by Air Speeded Post. Airmail rates are available on request.

Annual subscription rate 2002
Full text print version of the *BJA*
Full rate (institutions and individuals): UK and Europe £255, Rest of World US$400
Trainees: UK and Europe £120, Rest of World US$190
ESA/EACTA/EAA/ESRA/JSA/IARS members: UK and Europe £120, Rest of the World US$190
Single issue: UK and Europe £27, Rest of World US$38

Orders

Orders and payments from, or on behalf of, subscribers in the various geographical areas shown below should be sent to the office indicated. Payment may be made by the following methods: cheque (made payable to Oxford University Press); National Girobank (Account 500 1056); credit card (Mastercard, Visa, American Express); UNESCO coupons; direct debit (please ask for details). Bankers: Barclays Bank plc, PO Box 333, Oxford, UK; Code 20-65-18; Account 00715654.

The Americas: Oxford University Press Inc., 2001 Evans Road, Cary, NC 27513, USA.

Japan: available from the following agents:

Kinokuniya Company Ltd, Journal Department, PO Box 55, Chitose, Tokyo, 156 Japan.
Maruzen Company Ltd, Journal Division, PO Box 5050, Tokyo International, 100-31 Japan.
Usaco Corporation, 13-12 Shimbashi 1-chome, Minato-ku, Tokyo, 105 Japan.

Rest of the world: Oxford University Press, Journals Subscriptions Department, Great Clarendon Street, Oxford OX2 6DP, UK. Tel +44 (0)1865 267907; Fax: +44 (0)1865 267485; E-mail: jnl.orders@oup.co.uk

Please address orders and enquiries about availability as follows: *For current volume and back numbers from Vol. 82 onwards* to Oxford University Press.

For Vols 1-81 to Periodicals Service Company, 11 Main Street, Germantown, NY 12526, USA.
Tel: +1 (518) 537 4700; Fax: +1 (518) 537 5899.

Advertising

Advertising enquiries should be addressed to Peter Carpenter, PRC Associates, The Annexe, Fitznells Manor, Chessington Road, Ewell Village, Surrey KT17 1TF, UK. Tel: +44 (0)20 8786 7376; Fax: +44 (0)20 8786 7262; E-mail: mail@prcassoc.co.uk

© *The Board of Management and Trustees of the British Journal of Anaesthesia 2002*

All rights reserved; no part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise without the prior written permission of the *British Journal of Anaesthesia*, requests for which should be addressed to the Publisher, or a licence permitting restricted copying issued in the UK by the Copyright Licensing Agency Ltd, 90 Tottenham Court Road, London W1P 9HE, or in the USA by the Copyright Clearance Center, 222 Rosewood Drive, Danvers, MA 01923. For those in the US/Canada not registered with CCC, articles can be obtained by fax in 48 hours by calling: WISE for MedicineTM 1-800-667-WISE.

British Journal of Anaesthesia (ISSN 0007-0912) is published monthly by Oxford University Press, Oxford, UK. Annual subscription price is US$400. *British Journal of Anaesthesia* is distributed by Mercury International, 365 Blair Road, Avenel, NJ 07001, USA. Periodicals postage paid at Rahway, New Jersey, and additional entry points.

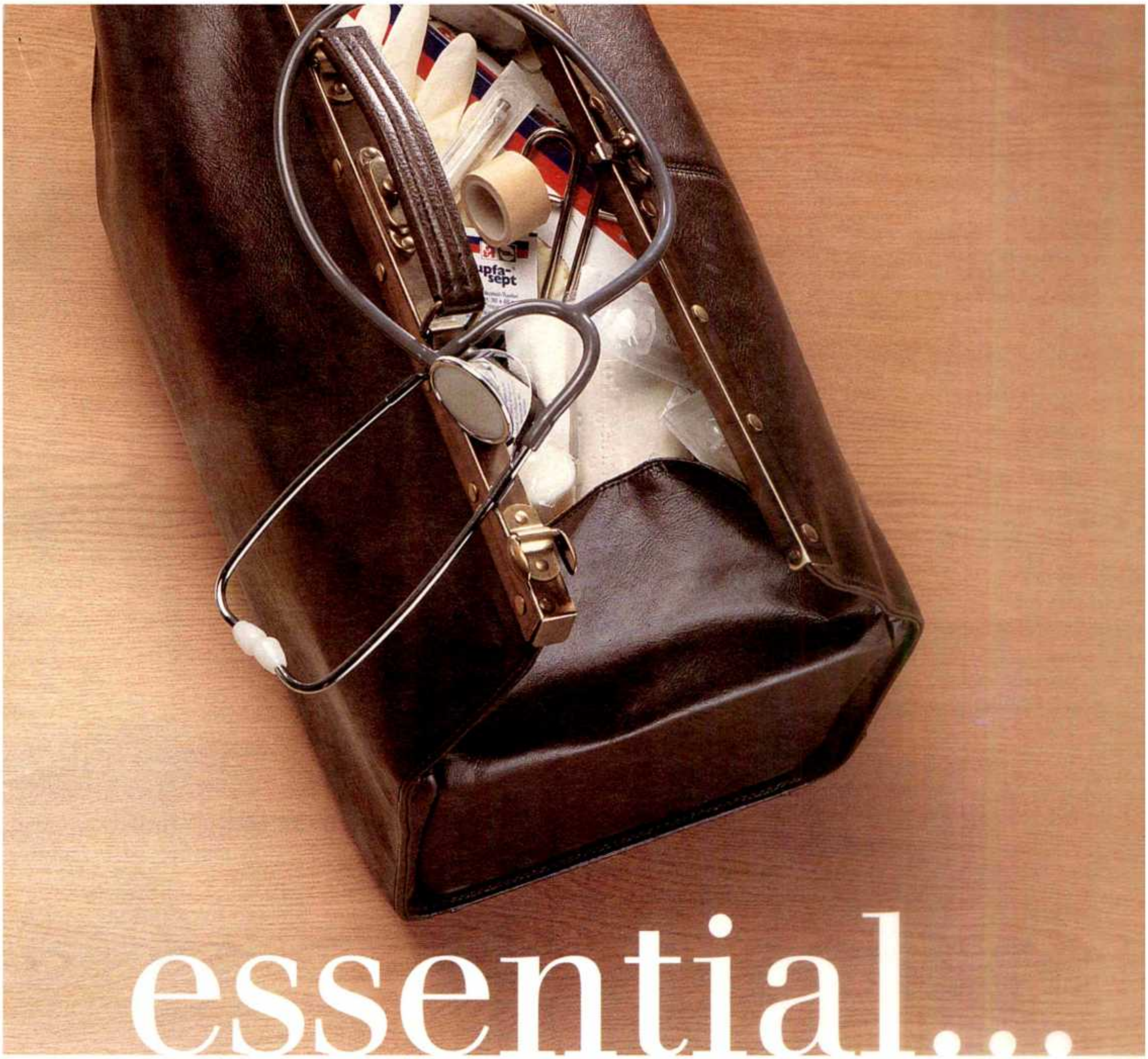
US Postmaster: send address changes to *British Journal of Anaesthesia*, c/o Mercury International, 365 Blair Road, Avenel, NJ 07001, USA.

Disclaimer

Whilst every effort is made by the publishers and editorial committee to see that no inaccurate or misleading data, opinions or statements appear in this Journal, they wish to make it clear that the data and opinions appearing in the articles and advertisements herein are the responsibility of the contributor or advertiser concerned. Accordingly, the publisher and the editorial committee and their respective employees, officers and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinions or statements. While every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described within this Journal, should only be followed in conjunction with the drug manufacturer's own published literature.

Printed by Information Press Ltd, Oxford, UK.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002



essential...

Editorial Notices

Important Notice to Authors

Electronic Submission of New Manuscripts to *The British Journal of Anaesthesia*

Please note that, from January 2003, the Editorial team requests that all new manuscripts (excluding Letters to the Editor and Book Reviews) be submitted electronically to the *British Journal of Anaesthesia* web site at:
http://bja.manuscriptcentral.com

Clear instructions for submission of new manuscripts are available on this web site. If these instructions are not adhered to, difficulty will be experienced in submitting new articles. For an interim period, manuscripts may also be submitted as hard copy to the Editor-in-Chief's office. It is envisaged, however, that this arrangement will be discontinued by the end of 2003.

Jennifer M. Hunter
Editor-in-Chief

Royal Medical Benevolent Fund

Are you a current or very recently retired doctor? Would you like to help colleagues less fortunate than yourself? Our recent cases include doctors who have suffered strokes, cancer, multiple sclerosis, paralysis after serious road accidents, blindness, schizophrenia, manic depression, dependency and the suicide of a partner. A growing number are junior doctors with limited pension entitlement and insurance cover.

Do you have a few hours to help?

Medical Liason Officer

The aim is to ensure doctors and their families in your area are aware of the financial help which may be available from the RMBF in time of crisis, and in particular to:

- Liaise with local hospitals, medical centres, medical societies and associations, to seek to ensure that doctors and their families are aware of the type of help the Fund may be able to provide.
- To provide information about the RMBF to any colleagues and their dependants likely to need assistance and to advise the Fund where appropriate.
- To advise the Fund of any planned medical conferences, exhibitions or meetings in your area where it might be possible for the RMBF to be represented.

We need career grade doctors who are currently practising or very recently retired (i.e. within the last two years), with good contacts within the medical world and able to commit on average a couple of hours a week to help the Fund.

For further information about becoming a volunteer Medical Liaison Officer for the Fund, please contact: Royal Medical Benevolent Fund, 24 King's Road, Wimbledon, London SW19 8QN. Tel: +44 (0)208 540 9194; E-mail: info@rmbf.org

National Acute Pain Symposium

Chester, UK, September 12–13, 2002

For further informaiton please contact: Georgina Hall, Department of Anaesthesia, Arrowe Park Hospital, Upton, Wirral, Merseyside CH49 5PE, UK. Tel: +44 (0)151 604 7056; Fax: +44 (0)151 604 7126; E-mail: georgina.hall@whnt.nhs.uk

Anaesthesia outside the square: CECANZ Conference 2002

Christchurch, New Zealand, September 18–20, 2002

For information, please contact: Conference Secretariat Joy Mehlhopt, Conference Innovators, PO Box 1370, Christchurch, New Zealand.

Tel: +61 3 379 0390; Fax: +61 3 379 0460; E-mail: joy@conference.co.nz. Website: www.cecanz2002.org.nz

Past, Present and Future of Jet Ventilation: Symposium and Workshop together with 2nd Annual Meeting and General Assembly of the European Society for Jet Ventilation

Friedrich Schiller University, Jena, Germany, September 20–21, 2002

For further information please contact: Mrs Marina Wolf, Department of Anaesthesiology and Intensive Care Medicine, Friedrich Schiller University Hospital, Bachstr. 18, D-07740 Jena, Germany. Tel: +49 3641 933642; Fax: +49 3641 933448; E-mail: kongress.kai@med.uni-jena.de; Website: http://www.med.uni-jena.de/anaesthesie

Société Française d'Anesthésie et de Réanimation

Annual congresses will take place in Palais des Congrés, Porte Maillot, Paris on the following dates:

September 26–29, 2002
September 18–21, 2003
September 20–October 3, 2004
September 29–October 2, 2005

For further information, please contact: SFAR, 74, rue Raynouard, F-75016 Paris, France. Tel: +33 1 45 25 82 25; Fax: +33 1 40 50 35 22; E-mail SFAR@invivo.edu

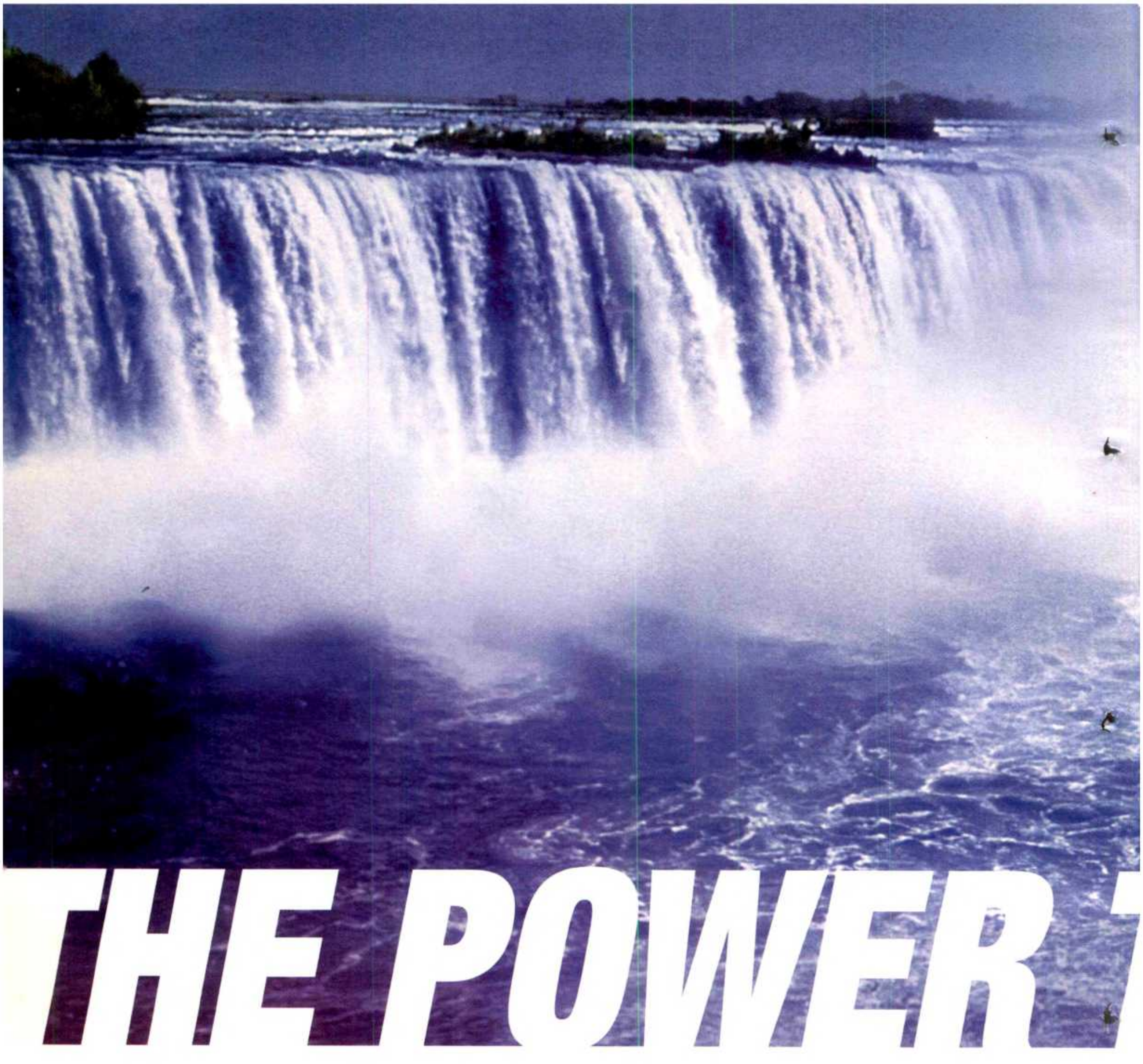
© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Out on call. All the essentials in the doctor's bag. In the OR. All the essentials from Primus. Dräger Medical's next-generation anesthesia workstation is designed to be your personal anesthesia assistant in the most demanding operations and in everyday clinic routine. With its advanced software Primus supports your decision-making for improved efficiency in low-flow delivery and parameter-setting. Primus also sets new standards in perioperative therapy with its new, innovative Intensive Care ventilator performance. A modular design, open-platform architecture and individual upgrade packages ensure you get a customized personal assistant to meet your specific requirements, with the patient monitoring system of your choice.
Primus allows you to enjoy optimized processes in the perioperative environment.

Primus is one of *three* pillars of innovation that mark a revolutionary new chapter in Dräger Medical's anesthesia device technology.

The essence of anesthesia.

Dräger
MEDICAL



NEW for the relief of pain an

RCOXIA® (etoricoxib)
BRIDGED PRODUCT INFORMATION

er to Summary of Product Characteristics before prescribing.

ESENTATION

ets: 60 mg, 90 mg and 120 mg tablets each containing 60 mg, 90 mg or 120 mg of etoricoxib ectively.

ES

ptomatic relief in the treatment of osteoarthritis and rheumatoid arthritis. Treatment of acute ty arthritis. Relief of chronic musculo-skeletal pain, including chronic low back pain. Relief cute pain associated with dental surgery. Treatment of primary dysmenorrhoea.

SAGE AND ADMINISTRATION

e orally with or without food.

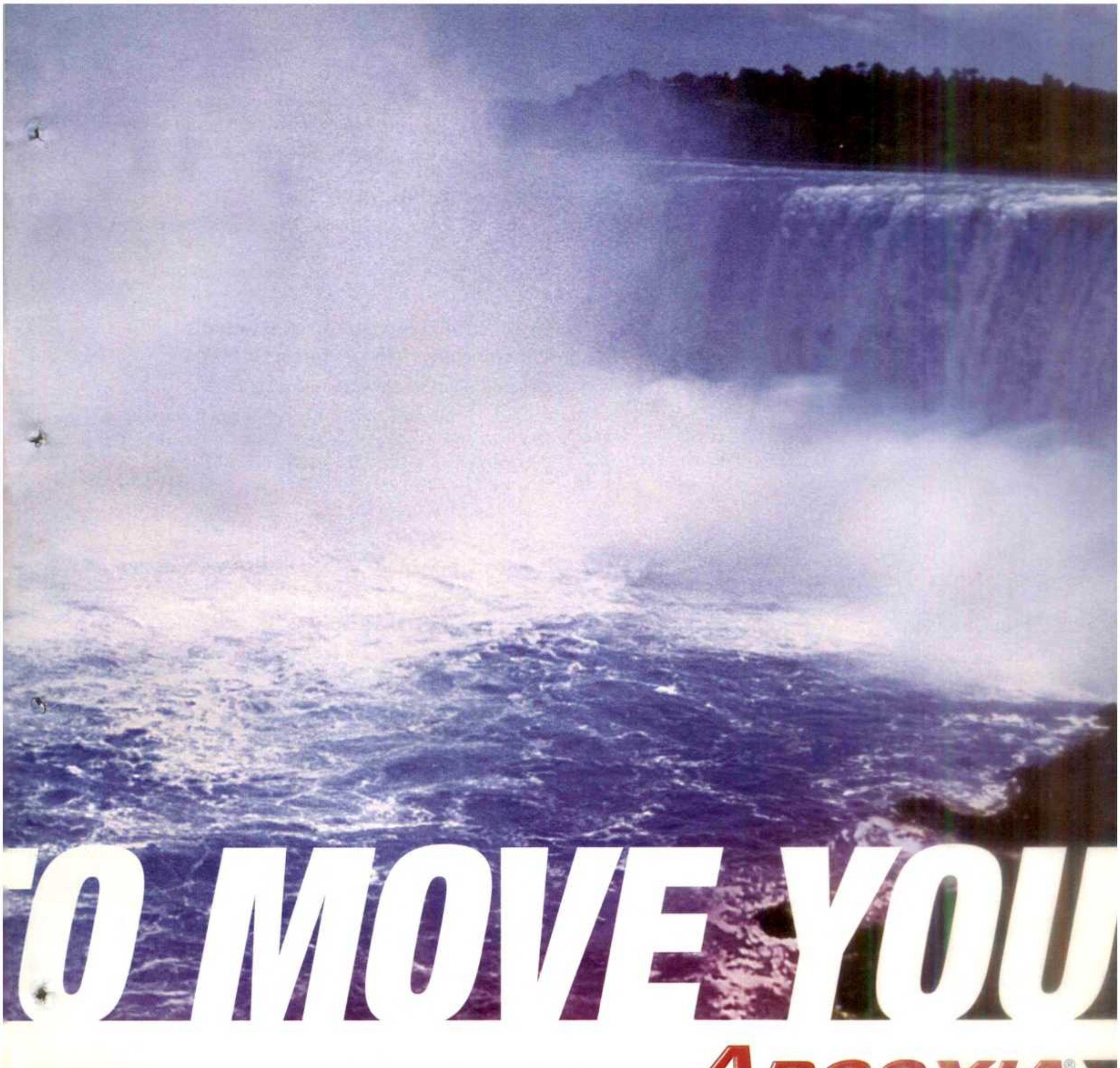
eoarthritis: 60 mg once daily. *Rheumatoid arthritis:* 90 mg once daily. *Acute gouty arthritis:* mg once daily for the acute symptomatic period only. *Acute pain associated with dental gery:* 120 mg once daily for the acute symptomatic period only. *Primary dysmenorrhoea:* ng once daily for the acute symptomatic period only. *Chronic musculo-skeletal pain including nic low back pain:* 60 mg once daily. Each dose above is the maximum recommended dose each condition. *Renal insufficiency:* No dosage adjustment necessary for patients with tinine clearance ≥ 30 ml/min. *Hepatic insufficiency: mild (Child-Pugh score 5-6):* do not eed a dose of 60 mg; *moderate (Child-Pugh score 7-9):* reduce the dose, **do not exceed 60 every other day.**

CONTRA-INDICATIONS

Hypersensitivity to any excipient of this product. Active peptic ulceration or gastro-intestinal (GI) bleeding. Severe hepatic dysfunction (Child-Pugh score >9). Estimated creatinine clearance <30 ml/min. Patients who have developed signs of asthma, acute rhinitis, nasal polyps, angioneurotic oedema or urticaria after aspirin or other NSAIDs. Pregnancy and lactation. Children under 16 years of age. Inflammatory bowel disease. Severe congestive heart failure.

PRECAUTIONS

Consider monitoring of renal function in patients with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis. Use caution when initiating treatment in patients with considerable dehydration. Rehydrate patients prior to starting therapy with etoricoxib. Exercise caution in patients with a history of cardiac failure, left ventricular dysfunction, or hypertension and pre-existing oedema from any other reason, as fluid retention and oedema have been observed in patients taking etoricoxib. Take appropriate measures, including discontinuation of etoricoxib where there is clinical evidence of deterioration in the condition of these patients. Etoricoxib does not inhibit platelet aggregation. Do not discontinue antiplatelet therapies and if indicated, they should be considered in patients at risk for or with a history of cardiovascular or other thrombotic events. Exercise caution in patients with a medical history of ischaemic heart disease. Take appropriate measures and consider discontinuing etoricoxib therapy if there is clinical evidence of symptomatic deterioration in the condition of these patients. Maintain appropriate medical supervision when treating the elderly and patients with renal, hepatic or cardiac dysfunction with etoricoxib. In clinical studies, some patients treated with etoricoxib, developed perforations, ulcers or bleeds (PUBs). Independent of treatment, patients with a history of GI perforation, ulcers and bleeding and those aged greater than 65 years are known to be at higher risk of a PUB. Elevations of ALT and/or AST (>3 times the upper limit of normal) have been reported in approximately 1% of patients treated in trials with etoricoxib 60 mg and 90 mg for up to one year. Evaluate any patient with symptoms /signs of liver dysfunction – or in whom an abnormal liver function test has occurred – for persistently abnormal liver function tests. Discontinue etoricoxib if persistently abnormal liver function tests (3 times the upper limit of normal) are detected. Etoricoxib may mask fever. Use of etoricoxib is not recommended in women attempting to conceive. *Interactions (pharmacodynamic): Warfarin:* closely monitor the prothrombin time INR when therapy with etoricoxib is initiated or the dose changed in patients receiving warfarin or similar agents, particularly in the first few days. *Diuretics and antihypertensive drugs:* NSAIDs may reduce the effect of diuretics and antihypertensive drugs. In some patients with compromised renal function, the co-administration of an ACE inhibitor and cyclo-oxygenase inhibitors may result in further deterioration of renal function, which is usually reversible. *Aspirin:* etoricoxib can be used concomitantly with aspirin at doses used for cardiovascular prophylaxis (low dose aspirin). However, concomitant administration of low dose aspirin with etoricoxib may result in an increased rate of GI ulceration or other complications compared to use of etoricoxib alone. Avoid concomitant administration of etoricoxib with doses of aspirin **above** those for cardiovascular prophylaxis, or with other NSAIDs. *Cyclosporin/tacrolimus:* monitor renal function when etoricoxib and either cyclosporin or tacrolimus is used in combination. *Interactions (pharmacokinetic). The effect of etoricoxib on the pharmacokinetics of other drugs: Lithium.* the plasma concentration of lithium could be increased by NSAIDs. *Methotrexate:* adequate monitoring is recommended for methotrexate-related toxicity when etoricoxib and methotrexate are administered concomitantly. *Oral Contraceptives (OC):* Administration of etoricoxib 120 mg



flammation in a broad range of indications

ARCOXIA® ▼

etoricoxib

with an OC containing 35 mcg ethinyl estradiol (EE) and 0.5 to 1 mg norethindrone for 21 days, either concomitantly or separated by 12 hours, increased the steady state $AUC_{0\text{-}24hr}$ of EE by 50 to 60%; however, norethindrone concentrations generally did not increase to a clinically relevant degree. Consider this increase in EE concentration when selecting an appropriate oral contraceptive for use with etoricoxib. *Digoxin:* Patients at high risk of digoxin toxicity should be monitored for an increase in digoxin C_{max} when etoricoxib and digoxin are administered concomitantly. *Effect of etoricoxib on drugs metabolised by sulfotransferases:* Etoricoxib is a weak inhibitor of human sulfotransferase activity, particularly SULT1E1 and has been shown to increase the serum concentrations of ethinyl estradiol. It may be prudent to exercise care when administering etoricoxib concurrently with other drugs primarily metabolised by human sulfotransferases (e.g. oral salbutamol and minoxidil). *Effect of etoricoxib on drugs metabolised by CYP isoenzymes:* Based on *in vitro* studies, etoricoxib is not expected to inhibit cytochromes P450 (CYP) 1A2, 2C9, 2C19, 2D6, 2E1 or 3A4. In a study in healthy subjects, daily administration of etoricoxib 120 mg did not alter hepatic CYP3A4 activity as assessed by the erythromycin breath test. *Effects of other drugs on the pharmacokinetics of etoricoxib:* The main pathway of etoricoxib metabolism is dependent on CYP enzymes. *In vitro* data indicate that CYP3A4 plays a major role (60%) in the metabolism of etoricoxib and that the remainder of the activity is shared among multiple other CYP isoenzymes. *Ketoconazole:* a potent inhibitor of CYP3A4, dosed at 400 mg once a day for 11 days to healthy volunteers did not have any clinically important effect on the single-dose pharmacokinetics of 60 mg etoricoxib (43% increase in AUC). *Rifampicin:* Co-administration of etoricoxib with rifampicin, a potent inducer of CYP enzymes, produced a 65% decrease in etoricoxib plasma concentrations. Consider this when etoricoxib is co-administered with rifampicin. *Antacids:* Antacids do not affect the pharmacokinetics of etoricoxib to a clinically relevant extent. *Pregnancy:* contra-indicated in the first, second and third trimesters of pregnancy. *Lactation:* contra-indicated.

SIDE EFFECTS

In clinical studies the following drug-related adverse experiences were reported at an incidence greater than placebo in patients with OA, RA or chronic low back pain treated with etoricoxib 60 mg or 90 mg for up to 12 weeks: *[Common (≥1/100, <1/10) Uncommon (≥1/1000, <1/100)]* ***Body as a whole/site unspecified:*** *Common:* abdominal pain, asthenia/fatigue, dizziness, oedema/fluid retention, flu-like disease. *Uncommon:* abdominal distention, chest pain, facial oedema, flushing, upper respiratory infection, creatine phosphokinase increased. ***Blood and the lymphatic system disorders:*** *Uncommon:* haematocrit decreased, haemoglobin decreased, leukocytes decreased, platelets decreased. ***Cardiovascular system:*** *Common:* hypertension. *Uncommon:* congestive heart failure, ecchymosis, non-specific ECG changes. ***Digestive system:*** *Common:* diarrhoea, dyspepsia, epigastric discomfort, heartburn, nausea. *Uncommon:* acid reflux, bowel movement pattern change, constipation, dry mouth, dysgeusia, oesophagitis, flatulence, gastro-enteritis, gastroduodenal ulcer, irritable bowel syndrome, oral ulcer, vomiting. ***Eyes, ears, nose and throat:*** *Uncommon:* blurred vision, epistaxis, tinnitus. ***Hepatobiliary disorders:*** *Common:* ALT increased, AST increased. ***Metabolism and nutrition:*** *Uncommon:* appetite change, weight gain. ***Musculoskeletal:*** *Uncommon:* muscular cramp/spasm, musculoskeletal pain/stiffness. ***Nervous system:*** *Common:* headache. *Uncommon:* insomnia, paraesthesia/hypesthesia, somnolence. ***Psychiatric disorder:*** *Uncommon:* anxiety, depression, mental acuity decreased. ***Respiratory system:*** *Uncommon:* cough, dyspnoea. ***Skin and skin appendages:*** *Uncommon:* pruritus, rash. ***Urogenital:*** *Uncommon:* urinary tract infection, blood urea nitrogen increased, hyperkalaemia, proteinuria, serum creatinine increased, uric acid increased. In addition, drug allergy has been reported rarely. The following serious undesira effects have been reported in association with the use of NSAIDs and cannot be ruled out etoricoxib: nephrotoxicity including interstitial nephritis and nephrotic syndrome and re failure; hepatotoxicity including hepatic failure and jaundice; gastro-intestinal toxicity includi perforation and bleeding; cutaneo-mucosal adverse effects and severe skin reactions.

PACKAGE QUANTITIES AND BASIC NHS COST

60 and 90 mg Tablets: packs of 28 tablets £22.96. 120 mg Tablets: packs of 7 tablets £5.

Marketing Authorisation numbers

Tablet 60 mg: PL 0025/0422. Tablet 90 mg: PL 0025/0423. Tablet 120 mg:PL 0025/04

Marketing Authorisation holder

Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, UK.

POM **Date of review:** April 2002

® denotes registered trademark of Merck & Co., Inc., Whitehouse Station, NJ, USA.

© Merck Sharp & Dohme Limited 2002. All rights reserved.

MSD
Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon, Hertfordshire EN11 9BU

Difficult Airway Day

Glenfield Hospital, Leicester, September 30, 2002

For further information please contact: Conference Co-ordinator, Clinical Education Centre, Glenfield Hospital, Groby Road, Leicester LE3 9QP, UK. Tel: +44(0) 116 250 2305; Fax: +44(0) 116 256 3334; E-mail: jackie.howarth@uhl-tr.nhs.uk

15th Annual Congress of the European Society of Intensive Care Medicine

Barcelona, Spain, September 29–October 2, 2002

Information: ESICM Congress Secretariat, 40 Avenue Joseph Wybran, B-1070 Brussels, Belgium; Tel: +32 2 559 03 55; Fax: +32 2 527 00 62; E-mail: public@esicm.org

Internet: http://www.esicm.org

Final FRCA Revision Course

Clinical Education Centre, Leicester Royal Infirmary, October 1–4, 2002

An intensive revision course of lectures, tutorials MCQ and SAQ papers and VIVA practice with individual feedback.

For further information, please contact: Christine Gethins. Tel: 0116 258 5291; E-mail: anae@le.ac.uk

Dingle 2002—4th Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 2–6, 2002

For further information contact: Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Crosspiece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

5th SW Thames Anaesthesia Forum

Da Balaia, The Algarve, Portugal, October 7–10, 2002

The scientific programme will include lectures and discussions on: acute and chronic pain; paediatric update; obstetric anaesthesia; neurology and anaesthesia; ITU and relevant medical topics; cardiothoracic anaesthesia; day case surgery; regional blocks; new drugs update; and training and education. There will be free papers; core topics for personal portfolio, guest speakers, workshops, videos on new drugs, equipment and techniques.

Open to all anaesthetists. Anaesthetists in training presenting papers are eligible for prizes. Deadline for abstracts: August 24, 2002. Meeting approved for CME. For full information and for online registration please visit: www.doctorsupdates.com

Dr J. B. Liban, Anaesthetic Department, St George's Hospital, Blackshaw Road, London SW17 0QT, UK. Tel: +44 (0) 208 725 3135; E-mail: liban@mailbox.co.uk

International Society for Anaesthetic Pharmacology (ISAP, formerly SIVA)

Orlando, Florida, USA, October 11, 2002

Contact: International Society for Anaesthetic Pharmacology (ISAP), 2 Summit Park Drive, Suite 140, Cleveland, OH 44131-2553, USA. Tel: +1 216 447 7862; Fax: +1 216 642 1127; E-mail: isaphq@iars.org; Website www.isaponline.org

Australian Society of Anaesthetists National Scientific Congress

Adelaide, Australia, October 26–30, 2002

This is the Society's premier scientific conference, held in an interesting part of the world.

For further details, please contact: Festival City Conventions, PO Box 949, Kent Town, SA 5071, Australia. Tel: +61 (0)8 8363 1307; Fax: +61 (0)8 8363 1604; E-mail: asa2002@fccconventions.com.au

8th International Congress of Cardiothoracic and Vascular Anesthesia

19th International Congress of the Israel Society of Anesthesiologists

Jerusalem, Israel, November 10–13, 2002

For further information regarding the Congress, please contact:

8th International Congress of Cardiothoracic and Vascular Anesthesia, PO Box 50006, Tel Aviv 61500, Israel

Tel: +972 3 5140000; Fax: +972 3 5140077; E-mail: anesth2002@kenes.com

Web address: http://www.isranest.org.il/congress 2002

Primary FRCA Revision Course

Clinical Education Centre, Leicester Royal Infirmary, November 27–29, 2002

An intensive revision course with emphasis on small group tutorial teaching and including MCQ and VIVA practice with individual feedback.

For further information, please contact: Christine Gethins. Tel: 0116 258 5291; E-mail: anae@le.ac.uk

The Transtec matrix patch is transforming pain management. Transtec is the first patch licensed for chronic, severe, non-malignant pain. Offering continuous pain relief from a 72-hour patch, Transtec is also associated with a low level of side-effects. So now when you're faced with the challenge of how to manage this type of pain, think square. Think patch. Think Transtec.

new

Transtec®

buprenorphine matrix patch

The first patch licensed for malignant pain and chronic, severe non-malignant pain

21st Annual Symposium: Clinical Update in Anesthesiology and Advances in Techniques of Cardiopulmonary Bypass with International Faculty and Industrial Exhibits

Antigua, West Indies, January 19–25, 2003

For information on abstracts, posters and free papers (deadline: November 4, 2002) please contact: Helen Phillips, Mount Sinai Medical Centre, 1 Gustave L. Levy Place, Box 1010, NY 10029-6574, USA. Tel: +1 212 241 7467; Fax: +1 212 426 2009; E-mail: helen.phillips@mssm.edu

77th Clinical and Scientific Congress of the International Anesthesia Research Society

New Orleans Marriott, New Orleans, Louisiana, March 22–26, 2003

For further information, please contact:

International Anesthesia Research Society, 2 Summit Park Drive, Suite 140, Cleveland, OH 44131-2553, USA. Tel: +1 216 642 1124; Fax: +1 216 642 1127; E-mail: iarshq@iars.org; Website: www.iars.org

German Congress of Anaesthesiology 2003

(DAK 2003)

Messezentrum Nürnberg, June 18–21, 2003

For further information, please contact:

Medizinisch Congressorganization Nürnberg AG.
Tel: +49 911 393160; Fax: +49 911 331204

27th Congress of The Scandinavian Society of Anaesthesiology and Intensive Care Medicine

Helsinki, Finland, August 16–20, 2003

A biannually arranged Scandinavian congress in one of the five Scandinavian countries; language: English.

For further information please contact: Prof. Per H.Rosenberg, Helsinki University Hospital, Helsinki FIN00029 HUS, Finland.

E-mail: per.rosenberg@hus.fi
Or: CONGREX/Blue & White Conferences Oy
E-mail: congrex@congrex.fi
Web address: www.congrex.fi

Dingle 2003—5th Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 1–5, 2003

For further information contact:

Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Crosspiece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

7th Biennial Congress of the Asian and Oceanic Society of Regional Anesthesia and Pain Medicine

Bangkok, Thailand, November 5–8, 2003

A biennial congress with a scientific programme of special lectures, symposiums, and workshops on various techniques of regional anaesthesia and pain medicine.

For further information, please contact: AOSRA Secretariat, 39 Pradipat 10 (Phaholyothin 11) phyathai, Bangkok 10400, Thailand. Tel: +66 0 2615 7301; Fax: +66 0 2615 7309; Mobile: +66 (01) 836 1368; E-mail: cdm@cdmthailand.com

Web address: http://www.cdmthailand.com

13th World Congress of Anaesthesiologists

Palais des Congrès de Paris, Paris, France, April 18–23, 2004

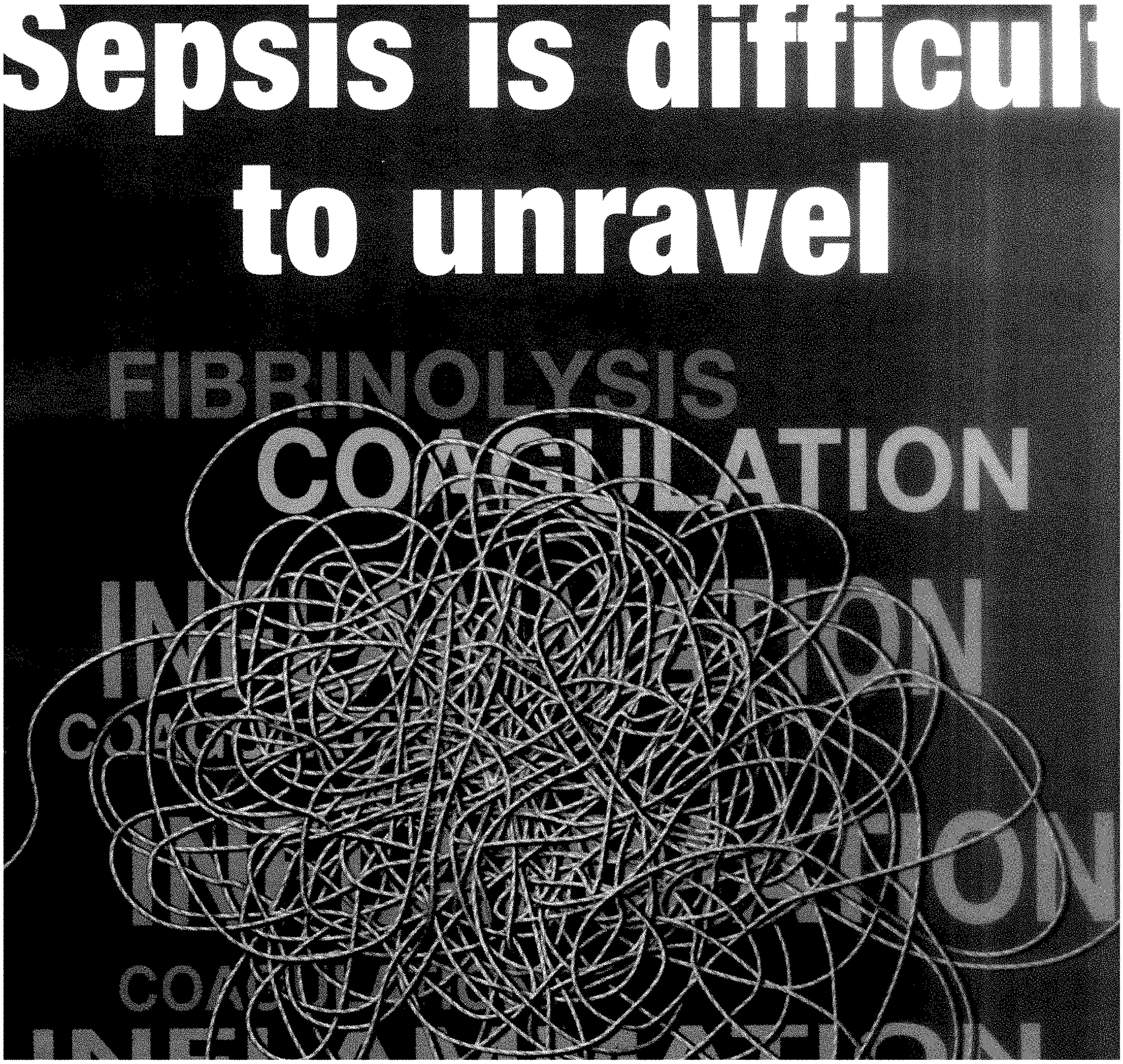
For further details, please contact the Congress Office at: COLLOQUIUM, 12 rue de la Croix Faubin, F-75557 Paris cedex 11, France. Tel: +33 (0) 1 44 64 15 15. Fax: +33 (0) 1 44 64 15 16/17. E-mail: wca2004@colloquium.fr
Website: www.wca2004.com

International Anaesthesia Research Society Annual Clinical and Scientific Congresses

78th Clinical and Scientific Congress of the International Anesthesia Research Society, Tampa Marriot Waterside Hotel, Tampa, Florida, March 27–31, 2004

79th Clinical and Scientific Congress of the International Anesthesia Research Society, Hilton Hawaiian Village, Honolulu, Hawaii, March 11–15, 2005

For information please contact: International Anesthesia Research Society, 2 Summit Park Drive, Suite 140, Cleveland, Ohio 44131-2553, USA. Tel: +1 16 642 1124; Fax: +1 216 642 1127; E-mail: iarshq@iars.org; Website: www.iars.org


Sepsis is difficult
to unravel
FIBRINOLYSIS
COAGULATION

EPREX® ABBREVIATED PRESCRIBING INFORMATION

Please refer to Summary of Product Characteristics (SmPC) before prescribing.

Presentation:
Epoetin alfa solution presented as 1,000 IU/0.5 ml, 2,000 IU/0.5 ml, 3,000 IU/0.3 ml, 4,000 IU/0.4 ml and 10,000 IU/ml in pre-filled syringes and 1,000 IU/0.5 ml, 2,000 IU/ml, 4,000 IU/ml and 10,000 IU/ml in vials. For subcutaneous (SC) injection.

Uses:
To increase autologous blood yield from adult patients in a predonation (ABD) programme (treat only patients with moderate anaemia if blood saving procedures not available or insufficient, when scheduled major elective surgery requires large blood volume). To reduce exposure to allogeneic blood tranfusions prior to major elective orthopaedic surgery (restrict use to patients with moderate anaemia, not having ABD, with expected moderate blood loss).

Dosage and administration:
ABD: IV route. Mildly anaemic patients (haematocrit 33-39%) requiring predeposit of ≥4 blood units: 600 IU/kg 2 times weekly for 3 weeks after the blood donation procedure, prior to surgery. Iron supplementation required.

Elective orthopaedic surgery: SC route. 600 IU/kg weekly three weeks prior to surgery and on surgery day. Where surgery lead time <3 weeks, 300 IU/kg ten consecutive days prior to surgery, on surgery day and for 4 days immediately after. Stop treatment if Hb level reaches 15 g/dl. Iron supplementation required.

Contra-indications:
Uncontrolled hypertension. All ABD programmes' contra-indications. Component hypersensitivity. Prior to major elective orthopaedic surgery in patients (not participating in an ABD programme) with severe coronary, peripheral arterial, carotid or cerebral vascular disease, including those with recent myocardial infarction or cerebral vascular accident. Patients who cannot receive adequate antithrombotic prophylaxis.

Warnings and precautions:
Closely monitor blood pressure. Epilepsy and chronic liver failure–use with caution. Consider and treat all other causes of anaemia before starting EPREX. Mostly, serum ferritin falls simultaneously with packed cell volume rise. Assure adequate iron stores to ensure optimum EPREX response. Monitor platelet count regularly during first 8 weeks. Epoetin alfa cannot be excluded as possible growth factor for any tumour type. Respect special warnings associated with ABD programme. Prior to elective orthopaedic surgery–establish anaemia cause and determine thromboembolic risk/benefit. Give adequate antithrombotic prophylaxis. If Hb >13 g/dl do not use; increased risk of thrombotic vascular events.

Use in pregnancy and lactation only if potential benefit outweighs potential risk to foetus or baby.

Side effects:
Nonspecific skin rashes and flu-like symptoms. Increased risk of thrombotic/vascular events where Hb >13 g/dl prior to elective orthopaedic surgery.

Overdosage:
High therapeutic margin. Phlebotomy may be performed if Hb too high.

Interactions:
Do not administer with other drug solutions. Potential cyclosporin interaction. No interaction evidence with G-CSF or GM-CSF.

Pharmaceutical precautions:
Store at 2 to 8°C. Do not freeze or shake. Protect from light. Unpreserved product. Administer only one dose per vial or syringe.

Legal category: POM.

Product licence/authorisation holder:
Janssen-Cilag Ltd, Saunderton, High Wycombe, Buckinghamshire, HP14 4HJ, UK.
(PL/0242/0215, 0218, 0221, 0297-9 PA/748/25/1-9)

Date of preparation: February 2000

Further information: Available from:
Janssen-Cilag Ltd, Saunderton, High Wycombe, Buckinghamshire, HP14 4HJ, UK.

APIVERSURGERY01022000

© Janssen-Cilag 2000 9/00 31553

EPREX® (epoetin alfa) Increases Preoperative Haemoglobin Levels[1,2]

EPREX Maintains Higher Postoperative Haemoglobin Levels[1,2]

Higher Haemoglobin Results In

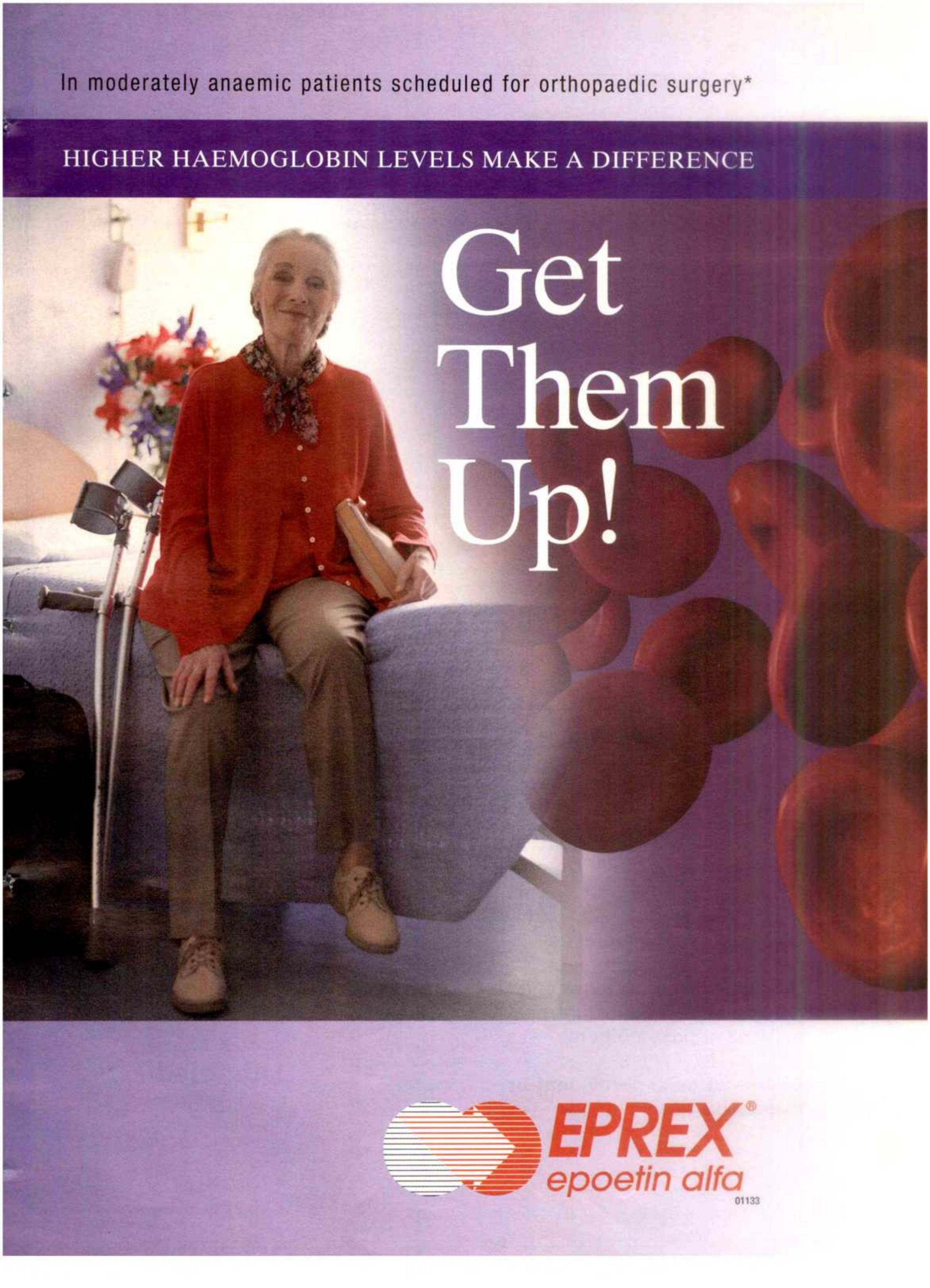
Reduction in transfusions[1,2]
Improved early postoperative vigour[3]
Earlier participation in rehabilitation[3]

EPREX Is Generally Well Tolerated

*Haemoglobin levels >10 to ≤13 g/dL.

References:
1. Stowell CP, Chandler H, Jové M, Guilfoyle M, Wacholtz MC. *Orthopedics.* 1999;22(suppl 1):s105-s112.
2. de Andrade JR, Jove M, Landon G, Frei D, Guilfoyle M, Young DC. *Am J Orthop.* 1996;25:533-542.
3. Keating EM, Ranawat CS, Cats-Baril W. *Orthopedics.* 1999;22(suppl 1):s119-s128.

Please see abbreviated Prescribing Information on adjacent page.



In moderately anaemic patients scheduled for orthopaedic surgery*

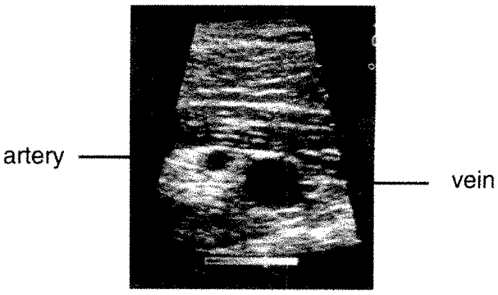
HIGHER HAEMOGLOBIN LEVELS MAKE A DIFFERENCE

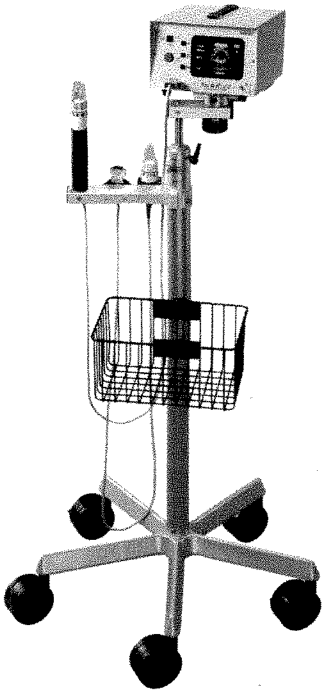
Get Them Up!

EPREX®
epoetin alfa
01133

SITE~RITE® 3

for real-time ultrasound-guided vascular access





NICE ONE!

Low Cost

Easy to use (See one, Do one, Teach one!)

See what you puncture

Significantly reduces risk of inadvertent arterial puncture, haematoma or pneumothorax

Choice of semi-permanent or disposable needle guides

Sole U.K. Distributor
Jade Medical
FREEPOST (RG2843)
Reading RG8 9ZZ
Tel:- 01491-874525
Fax:- 01491-874511
e-mail:-
sales@jade-medical.co.uk

"Site~Rite" is a registered trade mark of C.R. Bard, Inc., or an affiliate

Introducing

the first injectable COX-2 selective inhibitor

Pain relief with

Starting Power, Staying Power

Onset within 7 to 13 minutes[1]

Powerful, effective analgesia
Comparable onset of action and longer lasting efficacy compared to ketorolac 30 mg IV and 60 mg IM[2,3]

Fast acting and long lasting
Proven in a wide range of procedures, including orthopaedic, gynaecological and oral surgery[3,4,5]

No significant increase in bleeding time vs placebo in contrast to a traditional injectable NSAID[6]

Improved upper GI tolerability profile vs an injectable NSAID[7]

Lasts up to 12 hours[1]

New

Dynastat™ IV/IM

parecoxib sodium

Works fast...and lasts[1]

PHARMACIA

Abbreviated Prescribing Information DYNASTA

Presentation: Vials containing 40 mg parecoxib a powder for solution for injection or vials containin 40 mg parecoxib as powder for solution for injectio together with 2 ml ampoules 9 mg/ml (0.9% sodium chloride. Vials should be reconstituted with ml sodium chloride 9 mg/ml (0.9%) befor administration.

Indications: For the short-term treatment o postoperative pain.

Dosage: The recommended dose is 40 mg administere intravenously (IV) or intramuscularly (IM), followed every to 12 hours by 20 mg or 40 mg as required, not to excee 80 mg/day. *Elderly:* Usual dose may be used. For elderl patients weighing less than 50 kg, initiate treatment with hal the usual recommended dose and reduce the maximur daily dose to 40 mg. *Hepatic Impairment:* No dosag adjustment is generally necessary in mild hepatic impairment In moderate hepatic impairment (Child-Pugh scale 7-9) us with caution and at half the usual recommended dose an reduce the maximum daily dose to 40 mg. Not recommende in severe hepatic impairment (Child-Pugh scale >9). *Rena impairment:* Use caution in renal impairment or patients with fluid retention, however no dosage adjustment is usually necessary. *Children:* Not recommended.

Contraindications: Hypersensitivity to the active substance or to any of the excipients. Patients who have experienced bronchospasm, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria or allergic-type reactions after taking acetylsalicylic acid or NSAIDs or other cyclooxygenase-2 (COX-2) selective inhibitors. In the third trimester of pregnancy and breast-feeding. Severe hepatic impairment (Child-Pugh >9). Active peptic ulceration or gastro-intestinal bleeding. Inflammatory bowel disease. Severe congestive heart failure.

Warnings/Precautions: There is limited clinical experience with Dynastat treatment beyond two days and in certain types of surgery. Caution should be used in coronary artery bypass graft surgery as a higher risk of certain adverse events is observed. Caution in those with dehydration, impaired renal function, hypertension, compromised cardiac or hepatic function (moderate hepatic impairment). Dynastat may mask fever. Monitoring of incisions for signs of infection following surgery is advised. Caution in those with history of PUBs. Dynastat is not a substitute for acetylsalicylic acid (aspirin) in CV prophylaxis. Caution when used concomitantly with warfarin. Not recommended in women attempting to conceive.

Interactions: *Pharmacodynamic:* Monitor anticoagulant therapy due to increased risk of bleeding complications, however Dynastat does not affect pharmacodynamics of heparin. No effects observed on acetylsalicylic acid-mediated platelet aggregation. As for NSAIDs, may reduce the effect of diuretics, antihypertensives or increase risk of acute renal insufficiency. Monitor renal function when co-administered with NSAIDs, tacrolimus or cyclosporin. May be co-administered with opioid analgesics with a consequential reduction in the dose of morphine to achieve same level of analgesia. *Pharmacokinetics:* The dose of parecoxib sodium should be reduced when co-administered with fluconazole, a CYP2C9 inhibitor. No dosage adjustment is required when administered with ketaconazole (CYP3A4). Metabolism of the active moiety, valdecoxib may increase with enzyme inducers such as rifampicin, phenytoin, carbamazepine or dexamethasone. Caution should be observed with co-administration of medicines metabolised by CYP2D6 (eg. flecainide, propafenone, metoprolol), or substrates of CYP2C19 (eg. phenytoin, diazepam, imipramine). Monitor for methotrexate-related toxicity when given together. Lithium serum concentrations should also be monitored when given concomitantly as lithium clearance may be reduced. No kinetic or clinically significant effects have been observed when given together with injectable anaesthetics eg propofol or midazolam or inhalation anaesthetic agents nitrous oxide and isoflurane.

Adverse Effects: *Common (≥1/100, <1/10)* hypertension, hypotension, back pain, peripheral oedema, hypoaesthesia, alveolar osteitis (dry socket), dyspepsia, flatulence, creatinine increase, hypokalaemia, agitation, insomnia, postoperative anaemia, pharyngitis, respiratory insufficiency, pruritus, oliguria. *Uncommon (≥1/1000, <1/100)* aggravated hypertension, abnormal sternal serous wound drainage, wound infection, gastroduodenal ulceration, bradycardia, SGOT/SGPT increased, BUN increased, ecchymosis, thrombocytopenia, cerebrovascular disorder. The following rare, serious adverse events have been reported in association with the use of NSAIDs and cannot be ruled out for Dynastat: acute renal failure, congestive heart failure, anaphylactic shock, bronchospasm, hepatitis. Following coronary artery bypass graft surgery, patients administered Dynastat may have a higher risk of adverse events, such as cerebrovascular accident, renal dysfunction or sternal wound complication.

Packaging Quantity and Price:

Strength	Pack size	NHS price
40 mg (no diluent)	10	£49.60
40 mg (with diluent)	5	£28.34

Marketing Authorisation Numbers and Holder: EU/1/02/209/005 (10's) EU/1/02/209/008 (5+5's), Pharmacia Europe EEIG, Hillbottom Road, High Wycombe, HP12 4PX, UK.
Legal Category: POM.
Date of Preparation: April 2002.

References: 1. DYNASTAT SmPC 2002. **2.** Data on file. DYNASTAT Integrated Summary of Efficacy. 2000. Pharmacia Corporation, Peapack, NJ. **3.** Daniels SE, Grossman EH, Kuss ME *et al.* Clin Ther 2001;**23**(7):1018-1031. **4.** Langeland FF, Turpin M, Waller P *et al.* 2000 American Pain Society Abstract Database, Poster No. 814. **5.** Hubbard RC, Stulberg BN, Yoni S. ASA Meeting Abstracts. Abstract A-807. **6.** Data on file. DYNASTAT Integrated Summary of Safety Information. 2000. Pharmacia Corporation, Peapack NJ. **7.** Stolz RR Harris SI, Kuss ME *et al.* Am J Gastroenterol 2002;**97**(1):65-71

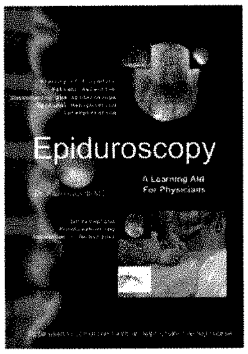
P7592/3/02

EPIDUROSCOPY

A learning aid for physicians

60 minutes of high quality digital video on DVD format

Includes sections on



- History of procedure
- Patient selection
- Introducing the scope
- Manipulating the scope in the epidural space
- Interpreting findings
- Interventional techniques
- Troubleshooting
- Anaesthetic considerations

Produced by Dr Paul Graziotti MBBS FFARACS FFARCS FFPMANZCA, Pain Management Physician

The perfect refresher tool for beginning and established practitioners.

Available for purchase at www.ipmt.net

---

go on-line

and visit our website

www.oup.co.uk

♦ for full information on all medical books from Oxford University Press, including the world-famous ***Oxford Textbooks*** and ***Oxford Handbooks***, an extensive list of medical textbooks, and authoritative reference works

www.oup.co.uk/medicine

♦ join our email information service to receive monthly news on new titles in your areas of interest

www.oup.co.uk/medicine/emailnews

♦ buy books on-line

MEDICINE FROM OXFORD

Abbreviated version of the International summary of product characteristics

Therapeutic indications* Esmeron is indicated as an adjunct to general anesthesia to facilitate tracheal intubation during routine and rapid sequence induction,and to provide skeletal muscle relaxation during surgery. Esmeron is also indicated as an adjunct in the intensive care unit (ICU) to facilitate tracheal intubation and mechanical ventilation. Contra-indications: Former anaphylactic reactions to rocuronium or to the bromide ion. Special warnings and special precautions for use: Since Esmeron causes paralysis of the respiratory muscles, ventilatory support is mandatory for patients treated with this drug until adequate spontaneous respiration is restored. As with all neuromuscular blocking agents, it is important to anticipate intubation difficulties, particularly when used as part of a rapid sequence induction technique. Although very rare, severe anaphylactic reactions to neuromuscular blocking agents, including Esmeron, have been reported. These reactions have, in some cases, been fatal. Due to the possible severity of these reactions, one should always assume that they may occur and take the necessary precautions. Dose levels greater than 0.9 mg rocuronium bromide per kg body weight may increase the heart rate; this effect could counteract the bradycardia produced by other anesthetic agents or by vagal stimulation. In general, following long term use of muscle relaxants in the ICU, prolonged paralysis and/or skeletal muscle weakness has been noted. In order to help preclude possible prolongation of neuromuscular block and/or overdosage it is strongly recommended that neuromuscular transmission is monitored throughout the use of muscle relaxants. In addition, patients should receive adequate analgesia and sedation. Furthermore, muscle relaxants should be titrated to effect in the individual patients by or under supervision of experienced clinicians who are familiar with their actions and with appropriate neuromuscular monitoring techniques. Because Esmeron is always used with other agents and because the occurrence of malignant hyperthermia during anesthesia is possible, even in the absence of known triggering agents, clinicians should be familiar with early signs, confirmatory diagnosis and treatment of malignant hyperthermia prior to the start of any anesthesia. In animal studies, Esmeron was shown not to be a triggering factor for malignant hyperthermia. The following conditions may increase the effects of Esmeron: Hypokalemia (e.g. after severe vomiting, diarrhea and diuretic therapy), hypermagnesemia, hypocalcemia (after massive transfusions), hypoproteinemia, dehydration, acidosis, hypercapnia, cachexia. Severe electrolyte disturbances, altered blood pH or dehydration should therefore be corrected when possible.
* Therapeutic indications may vary from country to country.

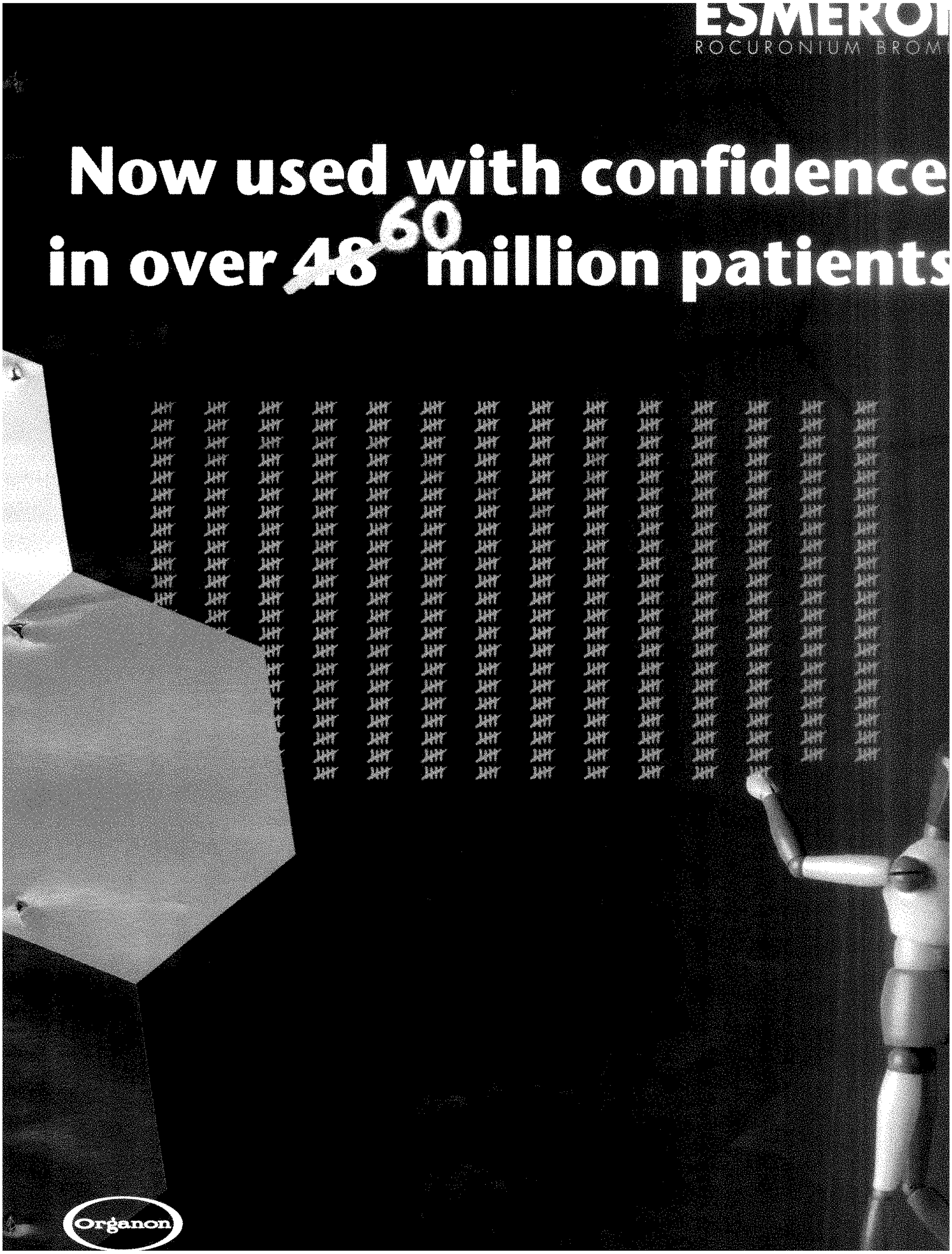
For full prescribing information see your local package insert.

December 1999

Organon

For further information, please contact:
N.V. Organon, PO Box 20, 5340 BH Oss, The Netherlands, www.organon.com

® Indicates trademark(s) registered in one or more countries.


ESMERO
ROCURONIUM BROM
Now used with confidence
in over ~~48~~ 60 million patients
Organon

Austrian International Congress and Rudolf Kucher Forum

2nd International Danube Symposium

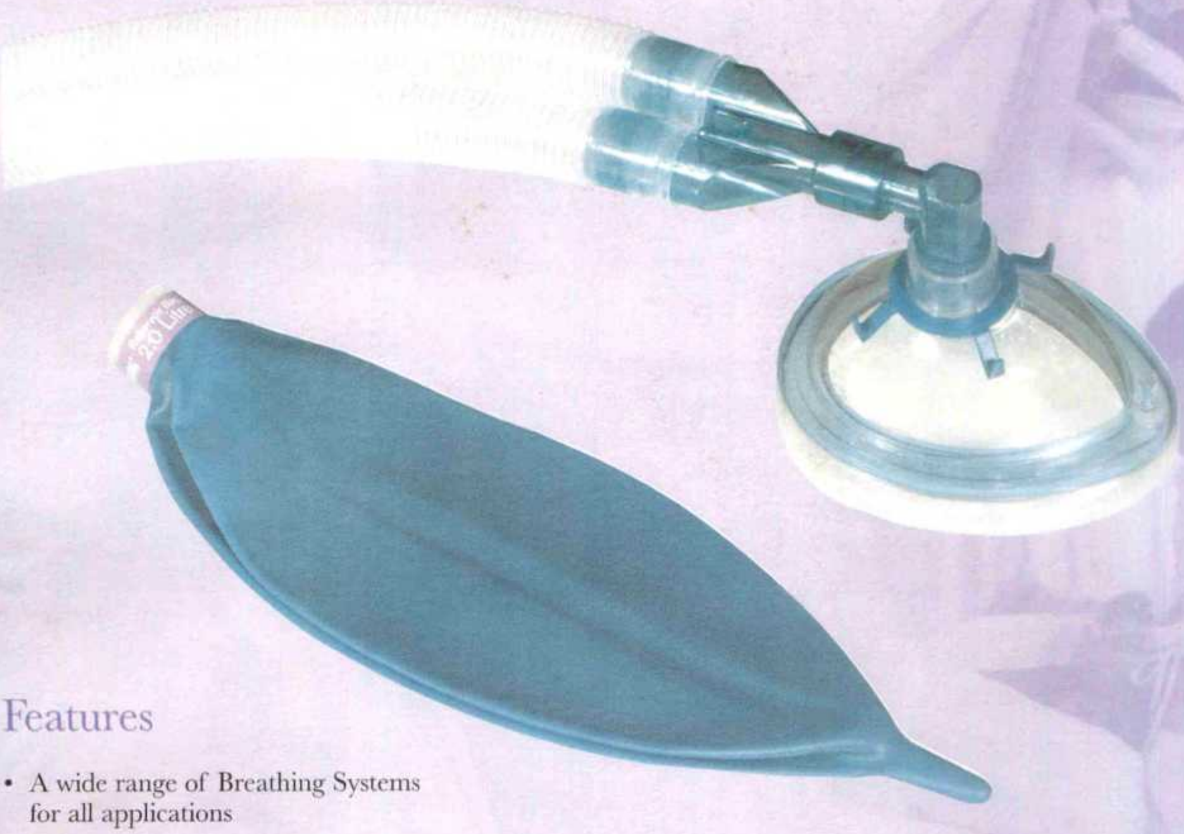
Anaesthesia & Intensive Care: Art or Science?
September 11–13, 2002 Vienna, Austria

Print copies of the meeting abstracts have been provided for Conference Delegates only. However, the abstracts will be available on-line to all BJA subscribers and are also freely available to all visitors to the following website from the date of the meeting (http://bja.oupjournals.org).

Print copies may be ordered from the Journals Subscriptions Department
(Email: jnls.cust.serve@oup.co.uk; Tel: +44 (0) 1865 353907; Fax: +44 (0) 1865 353485)
Price £27/US$42

Breathing Systems

for anaesthesia



Features

- A wide range of Breathing Systems for all applications
- Available in Flextube™, Smoothbore and Compact tubing
- Adult, Paediatric and Neonatal versions available

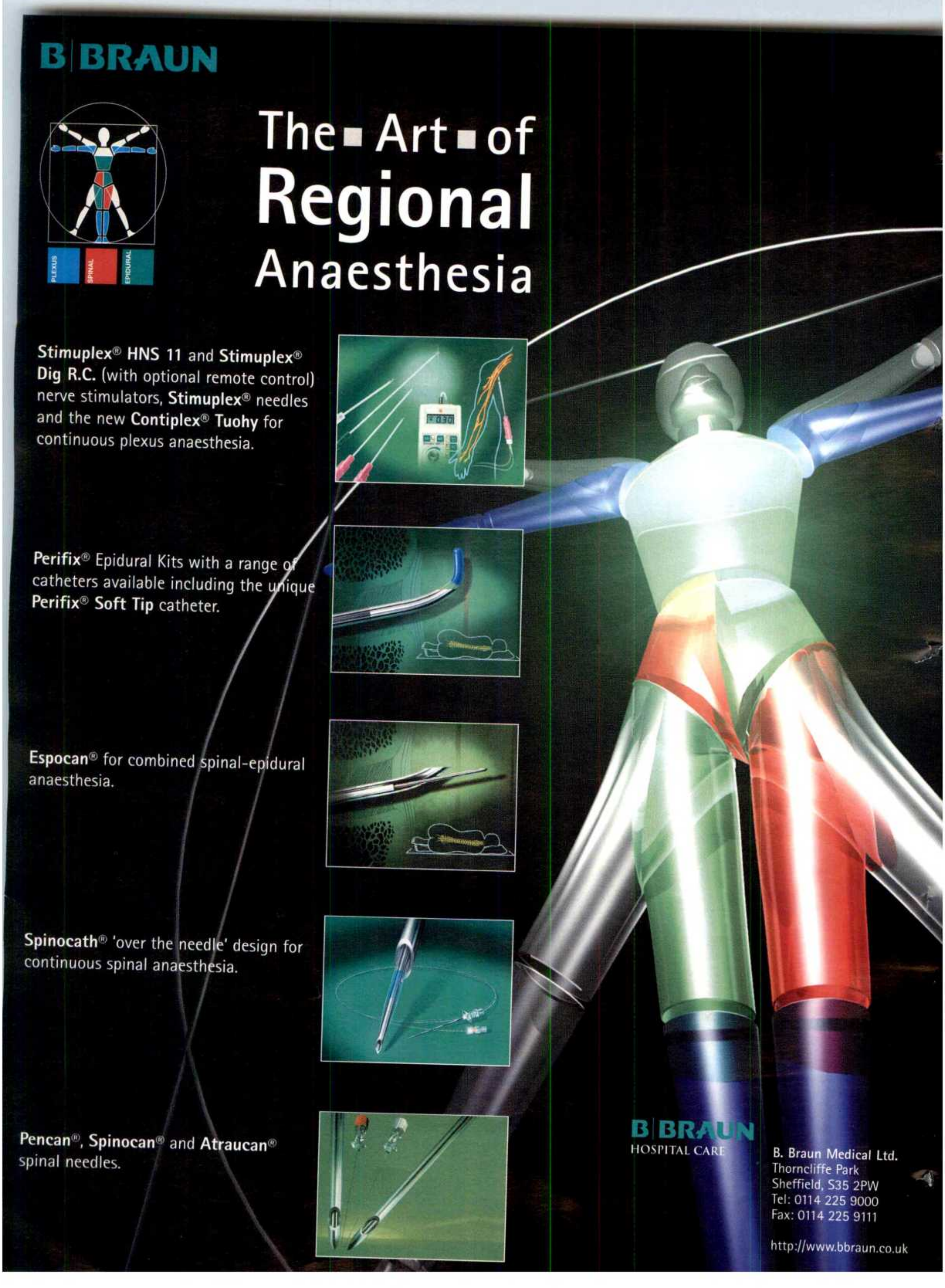
Intersurgical provide quality respiratory products that are designed for use in Anaesthetic Departments worldwide. We believe that every customer is important. Through our network of highly trained people we can provide you with a solution that will meet your needs, whilst providing an unrivalled level of support locally through our world wide offices.

For a quality service with a personal touch contact your local office or alternatively visit www.intersurgical.com

INTERSURGICAL®
COMPLETE RESPIRATORY SYSTEMS

Uni
M
T + 4
F + 4
info@

P25,803



B|BRAUN

The Art of Regional Anaesthesia

Stimuplex® HNS 11 and **Stimuplex® Dig R.C.** (with optional remote control) nerve stimulators, **Stimuplex®** needles and the new **Contiplex® Tuohy** for continuous plexus anaesthesia.

Perifix® Epidural Kits with a range of catheters available including the unique **Perifix® Soft Tip** catheter.

Espocan® for combined spinal-epidural anaesthesia.

Spinocath® 'over the needle' design for continuous spinal anaesthesia.

Pencan®, **Spinocan®** and **Atraucan®** spinal needles.

B|BRAUN
HOSPITAL CARE

B. Braun Medical Ltd.
Thorncliffe Park
Sheffield, S35 2PW
Tel: 0114 225 9000
Fax: 0114 225 9111

http://www.bbraun.co.uk

BJA

"I would have everie man write what he knowes and no more."—Montaigne

BRITISH JOURNAL OF ANAESTHESIA

Volume 89, Number 3, September 2002

Editorial I

Confidential enquiries into maternal deaths, 1997–1999†

The sixteenth of the triennial audits of the Confidential Enquiries into Maternal Deaths (CEMD) was published in December 2001,[1] and examined 378 cases. From 1952 until 1984, records of maternal mortality were produced separately for England and Wales, and Scotland. Since the 1985–1987 triennial report,[2] maternal deaths from these three countries have been combined and also include Northern Ireland, becoming a United Kingdom (UK) report.

A maternal death is defined by the *International Classification of Diseases: Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death* (ninth revision, ICD9) as 'the death of a woman while pregnant or within 42 days of termination of pregnancy from any cause related to or aggravated by pregnancy or its management, but not from accidental or incidental causes'.[3] A further revision[4] recognized that improved life support means that people may survive beyond 42 days after an event precipitating death and hence *late* deaths between 42 days and 1 yr after abortion, miscarriage, or delivery are also included.

The broad aims of the CEMD are to assess the main causes of maternal death, identify any avoidable or substandard factors, and inform health care professionals of the findings. It hopes that its recommendations will reduce maternal mortality and morbidity. A complicating factor is that there is no way of knowing how many pregnancies occur (indeed a woman herself may not know she is, or has been, pregnant). Therefore, the surrogate marker of maternities is used to estimate pregnancy denominator data. A maternity is a pregnancy that results in a live birth at any gestation or a stillbirth occurring at or after 24 completed weeks' gestation and is required to be registered by law. Therefore, the data are available, and should be accurate and consistent between successive reports.

How well have the aims to reduce maternal mortality and improve care been met? If we look at the death rates since the reports began, it is evident that they have. The overall maternal death rate in the 1952–1954 report[5] was 69 deaths per 100 000 maternities (England and Wales) compared with this report where the rate is 11.4 deaths per 100 000 maternities (UK). How much the reduced mortality is due to other factors than those described in the CEMD—such as better nutrition, medical advances, or pressures from other sources—is of course not possible to delineate.

The most marked improvement occurred in the 1950s and 1960s and although the improvement has appeared to level off, there has been better case ascertainment since 1994. Furthermore, it is important to appreciate that other factors associated with increased mortality are occurring in the childbearing population. For example, older mothers make up a larger proportion of maternities. In 1975, 6% of mothers were over 35 yr; in 1995, 11% were in this age category,[6] and in 2000, the proportion was 17%.[7] There has also been a dramatic increase in the Caesarean section rate the proportion of women delivered by this route doubled in the 1970s from 4% in 1970 to 9% in 1980, and in the year 2000 it was 21.3% in England.[7] Older women are also more likely to be delivered by Caesarean section.[7]

The improvements seen in anaesthesia are similarly dramatic. Until 1981, there were between 30 and 50 deaths in each triennium ascribed directly to anaesthesia. In the 1982–1984 triennium this figure was 19 deaths, between 1985 and 1996 (spanning four triennia and 12 yr), there were also 19 deaths. The reductions in mortality are in large part due to the recommendations in previous reports supported by the Obstetric Anaesthetist's Association and The Royal College of Anaesthetists.

The aim of the CEMD to disseminate its information is further enhanced this triennium by encouraging the publication of individual chapters in relevant specialist journals. The authors are grateful to the Editor-in-Chief of the *British Journal of Anaesthesia* for publishing the anaesthesia chapter in this issue.[8] This allows those readers in the UK who are not members of the Obstetric Anaesthetists' Association (whose UK members have received a copy of the report, another new initiative), and overseas readers to be aware of its findings and recommendations. The use of case vignettes is a popular feature of the chapters in the

---

†A copy of the full report of the Confidence Enquires into Maternal Deaths 1997–1999 can be obtained from the Royal College of Obstetricians and Gynaecologists bookshop (Tel +44 (0) 207 7726275, Fax +44 (0) 207 7245991), or from the online bookshop: www.rcog.org uk

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

CEMD reports, making for easy reading and understanding of the clinical context. The chapter highlights the cases where anaesthesia was felt to be the *direct* cause of death: it is noteworthy that in two of these cases, death was ascribed to anaesthetics given after prolonged and complex treatment in intensive care. Without the skill displayed in their intensive care management, these patients may not have survived to require these anaesthetics. The first case of the chapter is of particular importance because the final insult was the hypotensive effect of oxytocin (Syntocinon), whose correct dose and pharmacological effects are apparently poorly recognized. Many lessons are to be learned from the other cases illustrated, in some of which anaesthetists were not actually involved, but should have been.

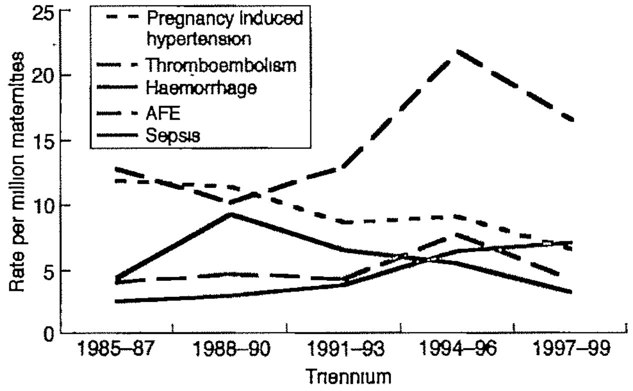


Fig 1 Death rates by major causes of direct deaths, United Kingdom 1985–1999 AFE, amniotic fluid embolus.

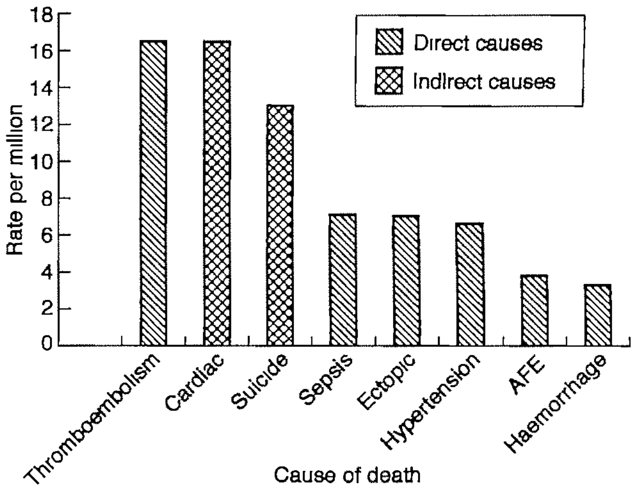


Fig 2 Major causes of maternal death United Kingdom 1997–1999. AFE, amniotic fluid embolus.

The importance of CEMD 1997–1999

Although all CEMD reports are important, the 1997–1999 report is possibly one of the most significant to have been published to date. For the first time, this report has been able to evaluate, more fully, other factors that may have played a part in the woman's death. These findings are of great concern, showing the maternal mortality rate among the most disadvantaged groups of society was about 20 times higher than among women in the highest two social classes. Women from ethnic groups other than white were, on average, twice as likely to die than women in the white group. A large number of these women spoke little English. There was also a disproportionate number of deaths from the traditional travelling community (such as gypsies). Alarmingly, 12% of women whose deaths are included in the report self-declared to a health care worker during their pregnancy that they were subject to violence in the home.

Other factors associated with an increased risk of death include young women under 18 yr, increasing maternal age, and increasing parity. Many women were obese. There also appeared to be over-representation of women with multiple pregnancies and those who had undergone *in vitro* fertilization. Although all these findings should be regarded with care, because the very small numbers involved mean they cannot be proven with statistical rigour, they nevertheless provide a unique indicator of the impact that social exclusion may have on a woman's reproductive health.

This report has also shown that the routine use of national guidelines can work. In this triennium, following the routine introduction and use of guidelines developed in part as a result of findings and recommendations from previous CEMD reports, there have been significant decreases in deaths from pulmonary embolism and sepsis following Caesarean section. In the very few cases where this occurred, guidelines do not appear to have been followed. Summaries of the major causes of direct maternal deaths for the years 1985–1999 are summarized in Figure 1.

Regrettably, though, women are still dying of potentially treatable conditions where the use of simple diagnostic guidelines may help identify conditions such as ectopic pregnancy, sepsis, and other cases of pulmonary embolism. The diagnosis of many of these cases was missed in the primary care or accident and emergency department setting.

For the first time, the number of *indirect* deaths from medical conditions exacerbated by pregnancy are greater than deaths from conditions that directly arise from pregnancy. In part, this increase may be explained by the greater number of women with life-threatening medical conditions that are exacerbated by pregnancy, such as primary pulmonary hypertension and cystic fibrosis, choosing to become pregnant. Deaths from cardiac disease are the joint leading cause with thromboembolism of maternal death reported to this enquiry, as shown in Figure 2, and continuing deaths from other medical causes including conditions such as epilepsy and diabetes also underline the need for multidisciplinary antenatal care and plans for delivery.

Psychiatric disorders

Although the chapter about deaths from psychiatric causes was only introduced for the first time in the 1994–1996 report,[9] its great social importance is reinforced in this triennium. Although these deaths are not recognized as maternal deaths by the International Classification of Diseases, and thus not counted in the overall maternal mortality rate for other countries, in the UK psychiatric deaths indirectly related to pregnancy are considered to be *indirect* or *late indirect* maternal deaths. This means they receive the attention and recommendations they deserve in this report. However, as a consequence, they inflate the UK maternal death rate when compared with other countries. In this triennium, psychiatric factors were found to be the second most common reported cause of maternal death, being associated with 12% of maternal deaths, with suicide accounting for 10% of maternal deaths. If the unreported deaths from suicide in pregnant women obtained from the Office of National Statistics are taken into account, suicide is in fact the leading cause of maternal death overall. The risk of suicide is 1 per 100 000 maternities. The suicides in this group of women are characterized by their violent nature, rather than overdose with psychotropic medication.

The chapters relating to deaths from thromboembolism, hypertensive disorders, and haemorrhage are of direct relevance to anaesthetists. The welcome return of the Caesarean section chapter, after its absence in the 1994–1996 report,[9] is also pertinent. The chapter on intensive care, first introduced in the 1991–1993 report,[10] is of equal interest. The main findings from these chapters are highlighted here.

Thromboembolism

The reduction of deaths from thromboembolism from 48 deaths (1994–1996) to 35 deaths in this triennium is gratifying. Of the 17 postpartum deaths from pulmonary embolism, 10 followed vaginal delivery. The other seven postpartum deaths followed Caesarean section, but in three of these cases the operation had been performed in an attempt to save the baby after massive antepartum pulmonary embolism. The reduction in deaths from this cause has occurred despite more women being at risk of thrombosis because of the rising Caesarean section rate. This improvement is ascribed to adherence to Royal College of Obstetricians and Gynaecologists guidelines on thromboprophylaxis published in 1995,[11] which have more recently been updated.[12] The recommendation from the 1994–1996 report,[9] is repeated with added emphasis; 'Wider use of thromboprophylaxis (*not only after Caesarean section*) and better investigation of classic symptoms (particularly in high risk women) are urgently recommended'. The importance of risk factors, such as family history of thromboembolism, obesity, long-term immobilization, and varicose veins, is emphasized.

Hypertensive disorders

The largest single cause of death among those women with pre-eclampsia and eclampsia was intracranial haemorrhage, reflecting a failure of antihypertensive treatment. There were five deaths after definite or probable eclamptic fits. Magnesium sulphate is the anticonvulsant of choice in eclampsia,[13 14] but its precise role in pre-eclampsia has yet to be established with clarity.[15] Hopefully, the situation will be clearer when the results of the multinational Magpie trial are reported in 2002.[16]

The HELLP syndrome, first identified as an entity in 1982,[17] where haemolysis, elevated liver enzymes, and low platelets complicate pre-eclampsia, was also responsible for five deaths in this triennium. The importance of anticipation of problems and multidisciplinary team working in this condition is emphasized.

Haemorrhage

The number of direct deaths due to haemorrhage has decreased from 9.2 per million maternities in 1988–1990, to 3.3 per million maternities. Of the seven deaths in this triennium due to antepartum and postpartum haemorrhage, three were due to placenta praevia, three to abruption of the placenta, and one to postpartum haemorrhage. A vignette illustrates the speed with which obstetric haemorrhage can become life-threatening where 60 units of blood were given in 2 h and 200 units given overall. This case emphasizes the need for women known to be at high risk of haemorrhage to be delivered at a hospital where blood and laboratory facilities, including haematological advice, are instantly available. Despite the caveats about the administration of Syntocinon earlier in this editorial, it is important to stress the need for effective oxytocic treatment where the need arises, as with atonic postpartum haemorrhage.

Caesarean section

One hundred and twenty women in the report were delivered by Caesarean section. The limitations of estimating fatality rates from Caesarean section are acknowledged. The data are observational and death is an amalgamation of the risk associated with the disorder for which surgery is indicated (such as pre-eclampsia or placenta praevia), and the risk associated with the procedure itself (including anaesthesia and perioperative care). Nevertheless, it is useful to note that if the risk of death from vaginal delivery is 1, the relative risk for all Caesarean sections is 4.9. The relative risk for elective Caesarean section is 2.3 compared with 12.0 when the Caesarean is performed because of immediate threat to the life of the mother or fetus. It is also pertinent that the relative risk of instrumental vaginal delivery is 3.1 compared with spontaneous vaginal delivery

Intensive care

Over 31% of deaths were recorded as requiring intensive care. The reasons for admission ranged from a short period of attempted resuscitation to up to 90 days intensive care and organ support for patients with hypoxic encephalopathy or multiple organ failure. The ongoing and possibly increasing problem of lack of availability of intensive care beds, and the need for transfer to these facilities from isolated maternity units, is highlighted.

The future of CEMD

Responsibility for the CEMD was transferred to the National Institute for Clinical Excellence (NICE) in 2000. NICE is reviewing the most appropriate format for this and the other confidential enquiries (those into stillbirths and deaths in infancy (CESDI), perioperative deaths, and homicides and suicides). NICE has proposed that in 2003 the CEMD will merge with CESDI to form a new Maternal And Child Health Confidential Enquiry. This would benefit the CEMD, in terms of increased administrative support, as this enquiry has always been undertaken on an extremely modest budget, representing enormous value for money. This is in a large part because of the whole-hearted support of the profession, particularly the regional assessors who give of their free time to evaluate the individual cases. It is vital that the current feeling of ownership of the CEMD is retained. Although still going through the consultation exercise, it is possible that the future format could include comparisons of deaths with near misses. For this to be successful, much better information systems than are currently available will be needed. It is further hoped to include pregnancy-based fields in the Intensive Care National Audit Research Centre (ICNARC) data set. If this is achieved, it would help identify some of the near misses. But this is currently done voluntarily by the participating intensive care units and is not all-inclusive.

G. M. Cooper
University Department of Anaesthetics and Intensive Care
Queen Elizabeth Hospital
Edgbaston
Birmingham B15 2TH
UK
G. Lewis
Department of Health
Wellington House
133–155 Waterloo Road
London SE1 8UG
UK
J. Neilson
University Department of Obstetrics and Gynaecology
Liverpool Women's Hospital
Liverpool L69 3BX
UK

References

1 *Why Mothers Die. Report on Confidential Enquiries into Maternal Deaths in the United Kingdom 1997–1999*. London: Royal College of Obstetricians and Gynaecologists, 2001
2 *Report on Confidential Enquiries into Maternal Deaths in the United Kingdom 1985–1987*. Department of Health, Welsh Office, Scottish Home and Health Department, Department of Health and Social Security, Northern Ireland. London: HMSO, 1991
3 World Health Organization. *International Classification of Diseases. Manual of the International Statistical Classification of Diseases, Injuries and Causes of Death. Ninth Revision, Vol. 1*. Geneva: WHO, 1980
4 World Health Organization. *International Statistical Classification of Diseases and Related Health Problems. Tenth Revision, Vol. 1*. Geneva: WHO, 1992
5 Ministry of Health. *Reports on Public Health and Medical Subjects No. 97. Report on Confidential Enquiries into Maternal Deaths in England and Wales 1952–1954*. London: HMSO, 1957
6 Government Statistical Service. *NHS Maternity Statistics, England: 1989–1990 to 1994–1995*. London: HMSO, 1998
7 Thomas J, Paranjothy S. Royal College of Obstetricians and Gynaecologists. Clinical Effectiveness Support Unit. *The National Sentinel Caesarean Section Audit Report*. London: Royal College of Obstetricians and Gynaecologists, 2001
8 Thomas TA, Cooper GM. Maternal deaths form anaesthesia. An extract from *Why Mothers Die 1997–1999*, the Confidential Enquiries into Maternal Deaths in the United Kingdom. *Br J Anaesth* 2002; **89**: 449–508
9 *Why Mothers Die. Report on Confidential Enquiries into Maternal Deaths in the United Kingdom 1994–1996*. Department of Health, Welsh Office, Scottish Home and Health Department, Department of Health and Social Security, Northern Ireland. London: TSO, 1998
10 *Report on Confidential Enquiries into maternal deaths in the United Kingdom 1991–1993*. Department of Health, Welsh Office, Scottish Home and Health Department, Department of Health and Social Security, Northern Ireland. London: HMSO, 1996
11 Royal College of Obstetricians and Gynaecologists. *Report of a Working Party on Prophylaxis Against Thromboembolism in Gynaecology and Obstetrics*. London: Royal College of Obstetricians and Gynaecologists, 1995
12 Royal College of Obstetricians and Gynaecologists. *Thromboembolic Disease in Pregnancy and the Puerperium: Acute Management. Guideline No. 28*. London: Royal College of Obstetricians and Gynaecologists, 2001
13 Duley L, Henderson-Smart DJ. Magnesium sulphate versus diazepam for eclampsia. *Cochrane Database Syst Rev* 2001; Issue 2
14 Duley L, Henderson-Smart DJ. Magnesium sulphate versus phenytoin for eclampsia. *Cochrane Database Syst Rev* 2001; Issue 2
15 Duley L, Gulmezoglu AM, Henderson-Smart DJ. Anticonvulsants for women with pre-eclampsia. *Cochrane Database Syst Rev* 2001; Issue 2
16 www.magpietrial.org.uk
17 Weiner L. Syndrome of hemolysis, elevated liver enzymes and low platelet count: a severe consequence of hypertension in pregnancy. *Am J Obstetrics Gynecol* 1982; **142**: 159–67

Editorial II

Pressure support ventilation and the critically ill patient with muscle weakness

The case reports by Kannan and colleagues[1] in this issue of *British Journal of Anaesthesia* serve to highlight that we should remain alert for inspiratory triggering failure during pressure support ventilation (PSV) in patients with severe muscle weakness. Despite improvements in the ability of ventilators to respond to the patient's own breathing pattern, inspiratory triggering failure may also be encountered in patients with chronic obstructive airways disease (COAD) or acute lung injury, who have high intrinsic positive end-expiratory pressure (PEEPi) in addition to possible muscle fatigue. There is also the potential for expiratory triggering failure and mismatches in tidal exchange in PSV.

Used for respiratory support and weaning, PSV has an inspiratory phase initiated by muscle effort (P_{mus}). The trigger—depending upon the machine and its options—is either the transient airway pressure drop below a set threshold, or the ventilator-sensed difference between the instantaneous inspiratory and expiratory flows, superimposed upon a base or bias flow commonly set to 10 litre min^{-1}. The flow 'sensitivity' setting of 2 litre min^{-1} may be considered to be equivalent to a pressure 'sensitivity' setting of 1 cm H_2O.[2] Whether at a flow sensitivity setting of 1 litre min^{-1} or at a pressure sensitivity of 1 cm H_2O, cardiogenic oscillations can result in spurious autotriggering in nearly one in five patients,[3] and even in the brain dead.[4] In contrast, when the trigger setting is less sensitive, triggering may fail in the presence of muscle weakness or impaired central drive. This could also occur when tracheobronchial secretions episodically increase the inspiratory resistance. Inspiratory triggering may fail in patients with a rapid respiratory rate and short expiratory time, and in patients with significant intrinsic PEEP and a corresponding delay in the fall in airway pressure on expiration. Deviation from the one to one response which is a ventilatory response following each breathing effort, increases at higher ventilatory frequencies and higher levels of pressure support and lower levels of patient effort.[5]

A less sensitive trigger setting will also tend to increase the work of breathing, although it has been pointed out that an inadequate flow rate delivery at the onset of inspiration, such as in the Tyco PB7200, was as significant in terms of increased respiratory work.[6] Some newer ventilators incorporate a rise time control to be used in conjunction with graphics to ensure rapid attainment of the pressure plateau, but if too rapid, over-pressure causes premature cut-out of the inspiratory phase.[7]

The tidal volume exchange in PSV is independent of inspiratory effort at the lowest levels of P_{mus} and neural expiration commences before the mechanical phase cycles to expiration.[5] Should respiratory demand increase, there is not invariably an increase in minute ventilation. If the patient is able to respond with a muscular effort equivalent to 5 cmH_2O (P_{mus}), there is no increase in tidal exchange but rather an increase in inspiratory flow rate with shortening of the mechanical inspiratory phase and an associated increase in the work of breathing. At greater levels of P_{mus}, when the timing of termination of neural and mechanical inspiration coincide, tidal exchange can increase by 50%. It can be imagined that satisfactory blood gases obtained during a period of high respiratory work may not be sustained either during sleep or if fatigue supervenes. Another study on patients and with computer simulation by the same team,[8] showed that there is a phase of great instability of tidal volume across changes in inspiratory P_{mus} between 3 and 12 cm H_2O, becoming more evident the greater the pressure support levels were above 10 cm H_2O. This is largely related to failed triggered breaths as the fall in ventilator breaths matched a paradoxical rise in tidal volume. Whilst the actual blood gases were thus similar in both the PSV and proportional assist ventilation (PAV) modes, the tidal volume and ventilator rate responses were only consistent in the PAV. However, this latter mode would probably provide totally inadequate tidal volumes at low levels of P_{mus}.

Determinants of the termination of the inspiratory phase vary according to the ventilators but typically they are a decline in the inspiratory flow rate to a fixed percentage of the peak flow rate, ranging between 5 and 25% (Siemens Servo900, Bird 8400ST), or to an absolute flow of 5 litre min^{-1} (Tyco PB7200). Most ventilators have a back-up means of terminating the inspiratory phase such as an over-pressure of 1.5 cm H_2O, or if the total inspiratory time exceeds 3 s or 80% of one breath cycle.[9]

Factors which may lead to a lag in inspiratory to expiratory cycling include both patient and circuit characteristics, such as a leak past the cuff of the tracheal tube. Ventilator-related factors are illustrated by the failure of the Tyco PB7200 to cycle at the target flow threshold in a workbench set-up; cycling was only initiated by over-pressure at end-inspiration.[9] Such an occurrence in patients will increase the work of breathing and contribute to an unsettled pattern of breathing. A terminal inspiratory pressure overshoot is diagnostic of the onset of neural expiration, except in the tetraplegic patient lacking expiratory muscle activity, in whom a weak inspiratory effort will also combine to extend the mechanical inspiratory time.

Being simple to set up, PSV has become widely used for the patient with an adequate ventilatory drive who is not so ill as to require muscular paralysis and controlled ventilation, especially as it probably prevents or helps restore deconditioned respiratory muscles,[10] and the patient does not appear to 'fight' the ventilator in the same way as with synchronized intermittent mandatory ventilation (SIMV). It has also been advocated for a faster weaning in comparison with SIMV, although a meta-analysis[11] has found spontaneous breathing trials equally effective, suggesting that adherence to procedures are as important as the actual weaning technique.

The multi-centre study of Estaban and colleagues,[12] enrolled 546 patients of whom a quarter were classed as difficult to wean on the first trial of spontaneous breathing. After randomizing the latter patients into four groups, the median time to wean differed by only a day or two; the two trials of spontaneous breathing groups weaned at 3 days each, the PSV group at 4 days and the synchronized intermittent mandatory ventilation group at 5 days. At 14 days, there were still between 10 and 20% who had failed to wean and no outcome was given for this group of slower patients.

Neurological disorders associated with profound respiratory muscle weakness include the gamut of acute weakness syndromes,[13 14] undiagnosed motor neurone disease,[15] and spinal cord injury. In one series, 62% of difficult-to-wean patients had neuromuscular abnormalities.[16] There were only two or three patients described as 'neurological' in each of the Estaban sub-groups and their individual progress was not documented. It leaves open the question of how best to mechanically ventilate and wean a tetraplegic patient, who may require weeks or months of respiratory support whilst avoiding diaphragm atrophy.

Diaphragm preservation in tetraplegia varies between the patient with only one functioning hemidiaphragm and the C5 transection patient with innervation of both diaphragms. In one study looking at the period of phrenic nerve function in 107 artificially ventilated tetraplegic patients, the 'early' group who never lost diaphragm activity after injury were fully weaned from ventilation by graduated ventilator-free breathing time after an interval of 37 (25) days mean (SD).[17] Peterson and colleagues[18] retrospectively studied 42 tetraplegics whose respiratory management alternated between the assist/control mode on the ventilator and increasing periods of ventilator-free breathing. They found that in these patients, without acute lung injury, final assist/control tidal volumes greater than 20 ml kg^{-1} were associated with a faster mean wean time of 37 as against 58 days, and attributed this to better prevention and clearing of atelectasis. It might, therefore, be prudent if PSV were used to include some deeper mandatory volume controlled breaths and, if necessary, incorporate a dead space to prevent hypocapnia.

Another reason for a mandatory back-up rate is that peripheral muscle fatigue in acute tetraplegia is associated with adaptive central fatigue,[19] which may manifest as periodic breathing or sleep apnoea. The tetraplegic patient who has lost all intercostal breathing has also lost the ability to share the work of breathing between the diaphragm and intercostal muscles, a pattern known as respiratory alternans, which predisposes to fatigue. A raised carbon dioxide blood gas tension in neurological patients breathing with CPAP or PSV is always indicative of muscle weakness or fatigue. Much can be gained by adopting an empirical bedside approach in which a value of the ratio of independent tidal volume to voluntary vital capacity of over 0.4 be predictive of fatigue,[20] assuming a degree of linearity between the volume and transdiaphragmatic pressure responses.

Sub-clinical and clinical muscle fatigue may be identified by the spectral shift in the EMG, but this technique is not widely available and the techniques of phrenic nerve stimulation, transdiaphragmatic and mouth occlusion pressures[13] are all relatively difficult. There is, however, a strong case to undertake more systematic electrophysiological studies of peripheral nerve and muscle in intensive care patients, in view of the finding that three-quarters of those with proven axonal polyneuropathy had diaphragmatic impairment, with reduction of the compound diaphragm action potential or increased latency of phrenic nerve conduction.[21]

In the clinical situation, it may be difficult to separate out the effect of central drive, peripheral fatigue, and simple muscle weakness whether in COAD or in neurological disease. Fluoroscopy of the diaphragm may be helpful, and the sniff test is reliable in pure tetraplegia as there is no paradoxical relaxation of the abdominal musculature on inspiration. Ultrasound examination may be more convenient but should be tempered by its limitations in visualizing the left hemidiaphragm and the possibility of false readings due to relative movements between the probe and abdominal wall.[22]

However, bedside neurological examination supplemented by regular spirometry of both tidal volume and vital capacity remains central to clinical appraisal of progress in weak patients. These measurements are integral to the technique of weaning by graduated ventilator-free breathing, with the prescribed rate of increase in ventilator-free time being adapted to the patient accordingly. In a slow wean, the patient benefits psychologically from his perceived active participation in the wean programme. Cuff deflation is also beneficial for clearance of mucus and for speech, all of which contribute to the success of this technique, even compared with the more widely known PSV.

J. W. H. Watt
Spinal Injuries Unit
Southport and Ormskirk Hospital NHS Trust
Town Lane
Southport PR8 6PN
UK

References

1 Kannan S, Sherwood N, Armfield A. Flow-induced hypoventilation in high spinal cord lesions—report of two cases Br J Anaesth 2002; 512–14

2 Hill LL, Pearl RG. Flow triggering, pressure triggering, and autotriggering during mechanical ventilation. *Crit Care Med* 2000; **28**: 579–81

3 Imanaka H, Nishimura M, Takeuchi, Kimball WR, Yahagi N, Kumon K. Autotriggering caused by cardiogenic oscillations during flow-triggered mechanical ventilation. *Crit Care Med* 2000; **28**. 402–7

4 Willatts SM, Drummond G. Brainstem death and ventilator trigger settings. *Anaesthesia* 2000; **55**: 676–84

5 Younes M. Proportional assist ventilation and pressure support ventilation: similarities and differences. In: Marini JJ, Roussos CS, eds. *Ventilatory Failure*. Springer Verlag, 1991; 361–80

6 Polesi G, Massara A, Poggi R. Brandolesi R, Brandi G, Rossi A. Flow triggering reduces inspiratory effort during weaning from mechanical ventilation. *Intensive Care Med* 1995; **21**: 682–6

7 Williams P, Muelver M, Kratohvil J, Ritz R, Hess DR, Kacmarek RM. Pressure support and pressure assist/control: Are there differences? An evaluation of the newest intensive care unit ventilators. *Respir Care* 2000; **45**: 1169–81

8 Giannouli E, Webster K, Roberts D, Younes M. Response of ventilator-dependent patients to different levels of pressure support and proportional assist. *Am J Respir Crit Care Med* 1999, **159**: 1716–25

9 Yamada Y, Du H-L. Effects of different pressure support termination on patient-ventilator synchrony. *Respir Care* 1998; **43**: 1048–57

10 Anzueto A, Peters JI, Tobin MJ *et al.* Effects of prolonged controlled mechanical ventilation on diaphragmatic function in healthy adult baboons. *Crit Care Med* 1997; **25**: 1187–90

11 Butler R, Kennan SP, Inman KJ, Sibbald WJ, Block G. Is there a preferred technique for weaning the difficult-to-wean patient? A systematic review of the literature. *Crit Care Med* 1999; **27**: 2331–6

12 Estaban A, Frutos F, Tobin MJ, *et al.* A comparison of four methods of weaning patients from mechanical ventilation. *N Engl J Med* 1995; **332**: 345–50

13 Polkey MI, Moxham J. Clinical aspects of respiratory muscle dysfunction in the critically ill. *Chest* 2001; **119**: 926–39

14 De Letter M-ACJ, Schmitz PAM, Visser LH, *et al.* Risk factors for the development of polyneuropathy and myopathy in critically ill patients. *Crit Care Med* 2001; **29**: 2281–6

15 Morales R, Mendizabal JE. Unrecognized motor neurone disease: an uncommon cause of ventilator dependency in the intensive care unit. *Respir Care* 1999; **44**: 434–6

16 Spitzer AR, Giancarlo T, Maher L, Awerbuch G, Bowles A. Neuromuscular causes of prolonged ventilator dependency. *Muscle Nerve* 1992; **15**. 682–6

17 Oo T, Watt JWH, Soni BM, Sett PK Delayed diaphragm recovery in 12 patients after high cervical spinal cord injury. A retrospective review of the diaphragm status of 107 patients ventilated after acute spinal cord injury. *Spinal Cord* 1999, **37**: 117–22

18 Peterson WP, Barbalata L, Brooks CA, Gerhart KA, Mellick DC, Whiteneck GG. The effect of tidal volumes on the time to wean persons with high tetraplegia from ventilators. *Spinal Cord* 1999; **37**: 283–8

19 Roussos A, Lakynthinos S. Ventilatory muscle fatigue and failure. In: Marini JJ, Roussos C, eds. *Ventilatory Failure*. Berlin. Springer Verlag, 1991, 125–52

20 Roussos CS, Macklem PT. Diaphragmatic fatigue in man *J Appl Physiol* 1977; **43**: 189–97

21 Zifko UA, Zipko HT, Bolton CF. Clinical and electrophysiological findings in critical illness polyneuropathy. *J Neurol Sci* 1998; **159**: 186–93

22 Cohen E, Mier A, Heywood P, Murphy K, Boultbee J, Guz A Excursion-volume relation of the right hemidiaphragm measured by ultrasonography and respiratory airflow measurements *Thorax* 1994; **29**. 885–9

British Journal of Anaesthesia 89 (3): 376–81 (2002)

BJA

CLINICAL INVESTIGATIONS

Impaired explicit memory after recovery from propofol/sufentanil anaesthesia is related to changes in the midlatency auditory evoked response

I. Rundshagen[1]*, K. Schnabel[2] and J. Schulte am Esch[3]

[1]Department of Anaesthesiology, University Hospital Charité, Campus Charité Mitte, Schumannstrasse 20/21, D-10117 Berlin, Germany. [2]Department of Psychology, University of Michigan, Ann Arbor, USA. [3]Department of Anaesthesiology, University Hospital Eppendorf, Hamburg, Germany

**Corresponding author*

Background. Midlatency auditory evoked responses (MLAER) can distinguish different stages of anaesthesia. We studied MLAER during emergence from propofol/sufentanil anaesthesia in relation to recovery of explicit memory.

Methods. MLAER were recorded in 29 healthy patients before and during anaesthesia and during emergence until the patients opened their eyes spontaneously. After a structured interview the next day, patients were classified into those with and without explicit memory of the recovery period. Latencies Na, Pa and Nb and the peak-to-peak amplitudes NaPa and PaNb were compared between the groups by multivariate analysis of variance. Results are mean (SD).

Results. At eye opening (37 (12) min after the end of anaesthesia) the latency Nb (47 (5) compared with 41 (5) ms; $P<0.001$) was prolonged and the amplitude PaNb (1.3 (0.8) compared with 1 (0.5) ms; $P=0.012$) was greater than the baseline value, respectively. The Nb latency was significantly shorter in patients with explicit memory (49 (2) ms compared with 45 (1); $P=0.041$).

Conclusions. Large intra- and inter-individual variability in the MLAER values limited their ability to predict memory responses in individual patients during emergence from propofol/sufentanil anaesthesia.

Br J Anaesth 2002; **89**: 376–81

Keywords: anaesthesia i.v., propofol; analgesics opioid, sufentanil; brain, evoked potentials; memory

Accepted for publication: April 24, 2002

Measurement of anaesthetic effects on the brain can assist more precise dosage and reduce side-effects. Values measured from the spontaneous electroencephalogram (EEG), such as the bispectral index, or from the evoked EEG, such as auditory evoked responses, may indicate anaesthetic effects during anaesthesia.[1] Auditory evoked responses (AER) are derived by averaging the EEG after repeated short auditory stimuli, which gives a highly reproducible sequence of waveforms. The brain stem auditory evoked responses (BAER) change little with anaesthetics.[2] The waveforms following the BAER components, the midlatency auditory evoked responses (MLAER), are more sensitive to anaesthetics, with characteristic changes in latencies and amplitudes.[3]

Several studies suggest that the MLAER can distinguish different states of consciousness. Davies and colleagues found consistent changes in MLAER latencies during repeated transitions from unconsciousness to consciousness during sedation with propofol in combination with spinal anaesthesia.[4] A threshold value of the MLAER latency Nb of 53 ms discriminated between the presence and the absence of an eyelash reflex with a sensitivity of 100% and a specificity of 96% during propofol sedation before surgery.[5] MLAER waveforms may indicate the ability to form

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

implicit memories.[6] An increase of the Pa latency of <12 ms distinguished patients with and without implicit memory after operation, with a sensitivity of 100% and a specificity of 77%.

We found that explicit memory performance in early recovery could be distinguished in patients waking up from isoflurane/nitrous oxide anaesthesia, using changes in the median nerve somatosensory evoked response (MnSSER) to indicate recovery of explicit memory.[7] The present study was designed to measure MLAER and explicit memory during recovery from propofol/sufentanil anaesthesia. We wished to compare the MLAER waveforms between patients with and without explicit memory for this time.

Methods

Patients

We studied 29 patients (18 males, 11 females; mean age 40 (18–61) yr, height 1.76 (0.10) m, weight 76 (12) kg; ASA I–II), scheduled for elective eye surgery lasting ~1 h, after approval from the local ethics committee and with written informed consent. We excluded patients with neurological diseases or hearing abnormalities, patients receiving centrally acting drugs, and those who had an ASA grade >II.

Anaesthesia and recovery

The patients received midazolam 7.5 mg p.o. for premedication 45 min before anaesthesia. After induction of anaesthesia with propofol 2 mg kg^{-1}, sufentanil 0.4 μg kg^{-1} and vecuronium 0.1 mg kg^{-1}, the trachea was intubated and anaesthesia maintained with propofol 8 mg kg^{-1} h^{-1}. The inspired oxygen concentration was 0.3. Additional doses of sufentanil 0.2 μg kg^{-1} were given when needed. At the end of surgery and after recording the MLAER, the propofol infusion was stopped. One hundred per cent oxygen was given using a fresh gas flow at 3 litre min^{-1} and the patients were extubated when breathing was adequate. After the extubation the patients received oxygen via a face mask.

Auditory evoked responses

MLAER recordings were made in a standard manner with an Evomatic 4000® system (Dantec, Copenhagen, Denmark). After defining the individual hearing threshold, a stimulus intensity of ~70 dB above this threshold was chosen and kept constant throughout the whole study. A random click to both ears via headphones was used. The stimulus frequency was 8 Hz. The MLAER waveforms were recorded on two amplifier channels using cup electrodes (zinc/lead) placed over Cz (international 10–20 system) and both mastoid bones. Impedances were kept below 5 kΩ. A bandpass of 0.02–2 kHz was used and 2000 stimuli were averaged for each response and stored on disk for later analysis. MLAER were analysed for 90 ms after the stimulus. During anaesthesia and recovery, a period of 180 ms post-stimulus was measured to detect excessive prolongation of the waveforms. The peak latencies of the brainstem component, V, of the two negative MLAER components, Na and Nb, and the positive peak Pa between were measured with a software package (EvoPC®; Müller, Hamburg, Germany). Peak-to-peak amplitudes NaPa and PaNb were measured.

Measurements

The patients were shown the procedure of MLAER recording on the day before surgery, and baseline values were obtained (Awake). Duplicate baseline recordings were performed. After surgery had finished, MLAER were recorded during steady-state propofol anaesthesia (Anaesth), and every 5–10 min during emergence from anaesthesia. Since the duration of recovery from anaesthesia varied from patient to patient, clinically comparable stages were defined for comparison of the MLAER components. Pre-EXT was defined as the last MLAER recording before extubation, Post-EXT as the first recording after extubation when the patients opened their eyes on command, and Recovery when the patients opened their eyes spontaneously and could state the name of an object shown to them.

Clinical measurements

We noted heart rate (beats min^{-1}), non-invasive mean arterial pressure (mm Hg), percutaneous oxygen saturation (%) and body temperature when MLAER were recorded. End tidal carbon dioxide partial pressure ($P\text{E}'_{CO_2}$) was measured during and after anaesthesia, and we noted the duration of anaesthesia, the time of extubation and the time of recovery.

Assessment of memory

When the patients had regained consciousness and opened their eyes spontaneously, they were asked to name precisely an object shown to them. A red booklet was opened and closed in front of them and they were asked to keep this booklet in mind. On the day after surgery a structured interview was used to assess the patients' memory of the immediate recovery period. A broad variety of questions were posed. The relevant questions are listed in Table 1. According to their responses the patients were classified into a group without recall (No-MEM) and a group with explicit recall for the immediate recovery period (MEM).

Table 1 Structured interview 24 h after anaesthesia

What was the first thing you remembered after waking up from anaesthesia?
Do you remember anything being shown to you when you woke up?
Do you remember whether you heard clicks?
Were you asked to remember anything during the time that you recovered?

Statistics

Latencies and peak-to-peak amplitudes NaPa and PaNb were calculated. The distribution of data was tested with the Kolmogorov–Smirnov test. The changes in the MLAER data were analysed using multivariate analysis of variance (ANOVA; Hotellings T-square; repeated measurement design) if the data were normally distributed. If the distribution was not normal, the data were analysed by non-parametric tests (Friedman test). All five measurements were included in a multivariate analysis giving a full two-factor-within design (three latencies × five time points). For descriptive purposes, *a posteriori* paired *t*-tests were used to compare MLAER components. We tested for correlation between the MLAER components, and the clinical measurements.

Inter-group comparisons for the MLAER components were made using multivariate ANOVA for repeated measurements (Hotelling's T-square) using Awake, Anaesth and Recovery values. Univariate comparisons were also made for the MLAER components at Awake, Anaesth and Recovery. The Wilcoxon test was used if a normal distribution was not present. $P<0.05$ was taken to represent significance for all statistical tests.

Results

Clinical findings and patient characteristics

Values are given as mean (SD). The surgical procedure lasted for 57 (26) min, and the total time of anaesthesia was 97 (28) min. Extubation was done 21 (9) min after the propofol infusion was stopped. The patients were able to identify the object shown to them 37 (13) min after the propofol infusion was stopped. Clinical measurements are listed in Table 2. The heart rate decreased during Anaesth and Pre-EXT compared with Awake, and the mean arterial blood pressure (MAP) decreased during Anaesth. Oxygen saturation, $P\acute{E}_{CO_2}$ and body temperature showed minor changes.

Two patients were not interviewed the day after surgery because they had been discharged. They were excluded from further analysis. Thirteen patients had explicit memory of the immediate recovery period, either recalling the shown object or the click stimulation of AER recording. Three of these patients recalled extubation. Fourteen patients did not remember anything of the study procedure. There was no difference in the characteristics or clinical measurements between these two memory groups. The dose of sufentanil, the duration of anaesthesia, the time to extubation and the duration of recovery showed no differences.

MLAER parameter during emergence from anaesthesia

The brainstem component V, which serves as a reference for an artefact-free recording, was identified in all patients when awake. The postauricular reflex was seen in some but not all of the patients, and the amplitudes could be seen to differ markedly. After this there were two negative and one positive waves of the MLAER in all patients except in two: one did not show the component Nb, and the other did not show the components Pa and Nb.

The assumption of a normal distribution for the MLAER latencies was supported by the Kolmogorov–Smirnov test. The amplitude NaPa was not normally distributed, so the amplitudes were analysed by non-parametric tests (the Friedman and Wilcoxon tests). Multivariate analysis showed a significant difference for the latency components comparing the different measurements ($P<0.001$). Moreover, a significant interaction between latency component and amplitude measurement indicated that the effect was more pronounced the longer the latency of the component ($P<0.01$). The absolute values of the MLAER latencies are shown in Figure 1. There were significant differences in the amplitudes NaPa and PaNb at the different

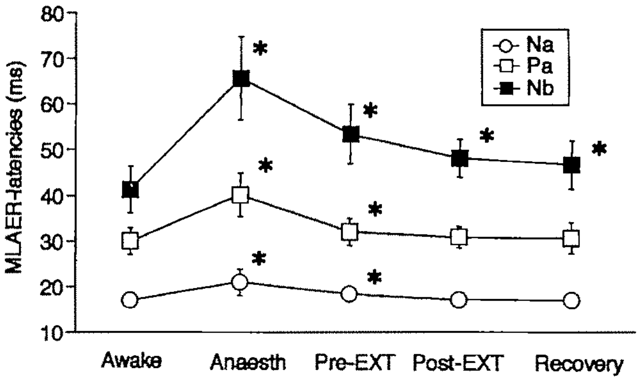


Fig 1 Means (SD) of MLAER latency components Na, Pa and Nb during the different measurements: awake, during propofol/sufentanil anaesthesia, before extubation, after extubation and at recovery. $^*P<0.05$ *vs* awake

Table 2 Clinical measurements Means (SD) of measurements when awake, during propofol anaesthesia, before extubation, after extubation and at recovery. MAP=mean arterial pressure, S_{O_2}=pulse oximeter reading, $P\acute{E}_{CO_2}$=end tidal carbon dioxide partial pressure Temperature was measured rectally

	Awake	Anaesth	Pre-EXT	Post-EXT	Recovery
Heart rate (beats min^{-1})	68 (13)	62 (11)	59 (9)	69 (12)	68 (11)
MAP (mm Hg)	93 (11)	86 (12)	90 (11)	100 (14)	96 (12)
S_{O_2} (%)	98 (1)	99 (1)	99 (1)	99 (1)	99 (1)
$P\acute{E}_{CO_2}$ (mm Hg)		35 (3)	36 (3)	43 (6)	41.2 (5)
Temperature (°C)	36.5 (0.4)	36.4 (0.3)	36.4 (0.3)	36.3 (0.3)	36.4 (0.4)

Table 3 MLAER latencies and amplitudes Data are means (SD) at awake, during propofol anaesthesia, before extubation, after extubation and at recovery *$P<0.05$ *vs* awake

	Awake	Anaesth	Pre-EXT	Post-EXT	Recovery
Latency Na (ms)	17.2 (0.3)	21.3 (0.6)*	18.8 (0.3)*	17.7 (0.4)	17.7 (0.3)
Latency Pa (ms)	30.1 (0.6)	40.4 (0.9)*	32.4 (0.6)*	31.4 (0.5)	31.3 (0.6)
Latency Nb (ms)	41.4 (1.0)	65.9 (1.9)*	53.7 (1.3)*	48.6 (1.0)*	47.3 (1.0)*
Amplitude NaPa (µV)	3.0 (0.6)	0.5 (0.1)*	1.3 (0.3)*	2.4 (0.6)	3.1 (0.6)
Amplitude PaNb (µV)	1.0 (0.1)	0.4 (0.1)*	1.0 (0.1)	1.4 (0.1)	1.3 (0.2)*

times ($P<0.001$). The absolute values for the peak-to-peak amplitudes are listed in Table 3.

The brainstem component V was seen during Anaesth with propofol in all patients. Compared with the awake measurements, the MLAER latencies were prolonged ($P<0.001$) and the amplitudes diminished ($P<0.001$). In three patients the component Nb was completely suppressed, and Pa was suppressed in one of these. These changes gradually reversed during recovery. Measurements were made before extubation in 26 patients. The latencies remained prolonged compared with awake ($P<0.05$), but decreased significantly compared with anaesthesia ($P<0.001$). The amplitudes of NaPa and PaNb increased significantly in comparison to anaesthesia, but NaPa remained reduced compared with awake ($P<0.001$).

After extubation MLAER were recorded in 20 patients, when the patients became responsive and opened their eyes at command. The latencies Na and Pa and the amplitudes regained baseline levels, but the latency Nb remained prolonged in comparison to before anaesthesia ($P=0.001$). When the patients opened their eyes spontaneously, MLAER components were seen in all patients again, except Pa, and Pa and Nb in the patients who did not have these components before anaesthesia. The latency Nb remained prolonged in comparison to preoperative measurement ($P<0.001$). The amplitude PaNb exceeded the baseline value ($P<0.05$).

MLAER measurements and memory

There was no difference between MLAER values before surgery between patients who later had explicit recall ($n=13$) and those who did not ($n=14$). The time of anaesthesia, time to extubation, duration of recovery and the dose of sufentanil were not different between the groups. At Recovery, in contrast, the latency of Nb was significantly less in the patients with explicit memory compared with the patients without (49.3 (1.8) ms *vs* 44.9 (1.3); $P=0.041$). The other MLAER components did not differ. Figure 2 shows two original AER traces at Awake and Recovery: one from a patient without and one with explicit memory. The individual Nb latencies at Awake and Recovery for the two memory groups are shown in Figure 3. Eleven data points only are shown for the group MEM, because two patients in that group did not have an Nb component during Awake and Recovery.

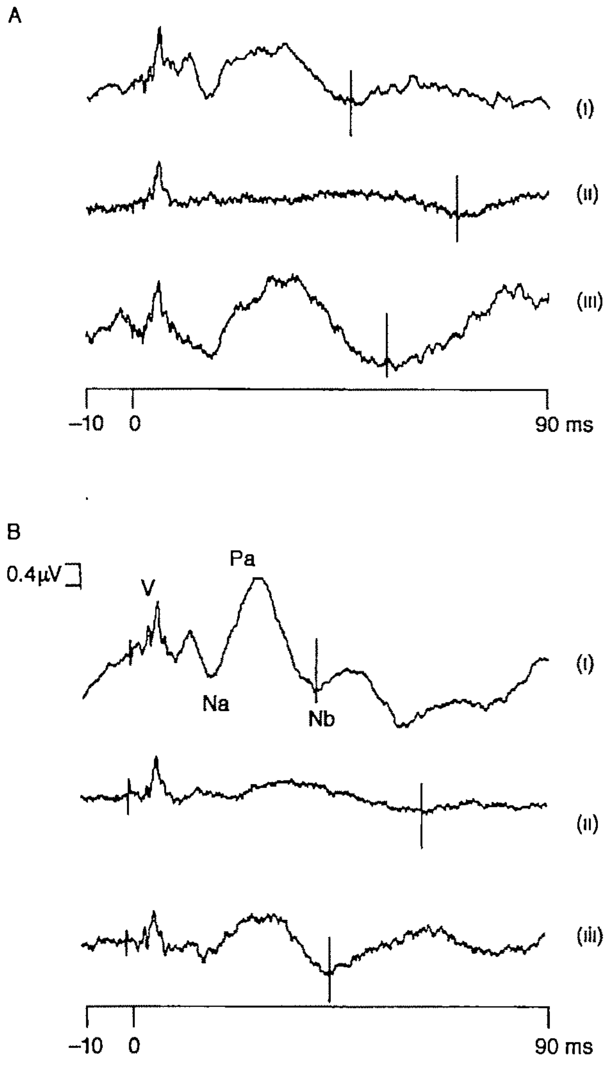


Fig 2 AER tracings of two patients The brain stem component V and the three midlatency components are indicated The upper traces (A) show the AER of a female patient who did not remember recovery. The lower traces (B) show the AER of a male patient who had explicit memory The different measurements are (i) awake, (ii) during propofol/sufentanil anaesthesia after surgery, and (iii) when the patients opened their eyes spontaneously. Vertical lines indicate the Nb latencies EEG-Montage Cz *vs* linked mastoid, binaural click stimulation

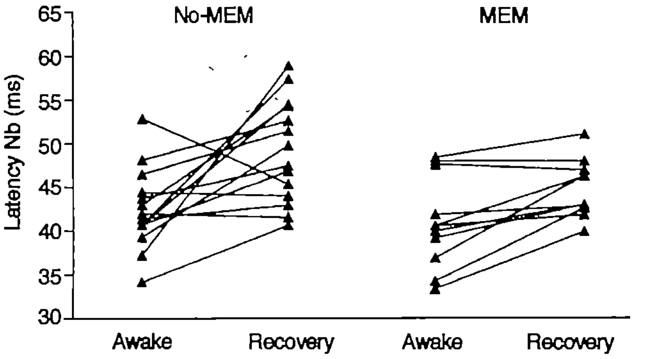


Fig 3 The individual Nb latencies are indicated at awake and at recovery, when the patients opened their eyes after anaesthesia. The patients of the group No-MEM did not remember recovery, while the patients of the group MEM had explicit recall

Discussion

We found graded changes of MLAER during emergence from anaesthesia. The anaesthetic-induced changes in the MLAER recovered when the patients regained consciousness and were able to identify an object correctly. The persistent increase in the latency Nb indicated impaired processing of auditory signals 38 min after anaesthesia with propofol/sufentanil. The latency of Nb was shorter in the patients who had explicit recall compared with patients without explicit memory.

These findings support previous reports that BAER and MLAER show a decrease in the amplitudes and an increase in latencies during anaesthesia.[2 8 9] BAER and MLAER were measured during increments of anaesthesia with propofol.[10] In contrast to the BAER, the MLAER were affected markedly by propofol (7 mg kg^{-1} h^{-1}), and latencies and peaks could not be measured. This is in contrast to the present study, where Nb was completely suppressed in three patients and Pa was suppressed in one patient only. Depression of MLAER is in part reversed during surgical stimulation, which could explain these different results.[11 12]

Tooley and colleagues used MLAER changes to establish a dose response curve using propofol as a sole agent in patients without surgical stimulation.[5] A cut-off value of 53 ms for the Nb latency had a sensitivity of 100% and a specificity of 96% as a discriminator of eyelash response *vs* no response. Concentrations >6 µg ml^{-1} attenuated the auditory response to an extent that made it difficult to determine the components. Care was needed to obtain AER in awake patients without premedication, because muscle artefact affected the signal. Coherent averaging gave the most reliable estimate of the AER. In the present study we recorded MLAER the day before surgery to familiarize the patients with the procedure, and repetitive stimulation reduced the effect of muscle artefact. We could not obtain MLAER during and immediately after extubation because of muscle artefact. During recovery the averaging time was sometimes prolonged because artefacts were present. Coherent averaging might have improved the extraction of MLAER during recovery. The mean latency of Nb was ~54 ms, when the patients were tolerating the tracheal tube immediately before extubation. It decreased to ~48 ms after extubation, when the patients opened their eyes at command, which supports the observations of Tooley and colleagues.[5] Our study does not indicate a clear threshold because of the large inter-individual overlap in the Nb data. Muscle artefacts during recovery could affect visual interpretation of the components. However, large inter-individual differences in the MLAER components have been described in the awake state, and MLAER are rarely used to diagnose hearing problems.[8 13]

In a previous study we recorded median nerve somatosensory-evoked responses during emergence from anaesthesia.[7] When the patients identified an object shown to them when waking from anaesthesia, the amplitude P25N35 exceeded the awake value. In the present study the amplitude PaNb was greater than the awake values. These changes may reflect an effect of cortical arousal by surgery, but several factors may contribute to the results. The patients had received midazolam for premedication and sufentanil intraoperatively.

In contrast to the increase in amplitudes, a persistent delay in the latency Nb was found to be present when the patients had regained consciousness, which could be related to explicit memory performance. In previous studies with median nerve somatosensory-evoked responses we found that midlatency MnSSER components were prolonged and correlated with explicit memory.[7 14] The cortical components of evoked responses, >30 ms post-stimulus, are more sensitive to residual anaesthetics than the earlier components and need more time to recover, irrespective of the stimulation mode. These indicate impairment of more complex cognitive processing such as implicit or explicit memory processing. The coherent frequency of the AER could be related to categorical memory tests during isoflurane administration.[15] During sedation with propofol, memory performance correlates more strongly with changes in AER amplitude P3 than with the drug concentration.[16] However, AER components may not reliably indicate memory during different states of consciousness.[17] Irrespective of the significant group effects, our results suggest a low predictive value because the inter-individual variation of Nb latency is considerable.

Computer-assisted measurements of the AER, such as the AER index or use of moving averaging techniques, have been developed.[18 19] During recovery from an induction dose of propofol, concentration-related effects on the AER index were found, but a threshold was found in seven of 22 patients.[20] The AER index returned to awake levels only when the patients had already developed clinical signs of arousal. In 10 female patients anaesthetized with propofol and nitrous oxide, there was no difference between the awake AER index and the values when the patients opened their eyes at command.[21] Further studies are needed to show if the predictive value of the MLAER is improved by computer-assisted techniques. As Thornton states: "A brain signal recorded at one point in time will not necessarily predict future behaviour accurately if events or treatments which occur in the period between the two time points can influence behaviour" [3]

References

1 Drummond JC. Monitoring depth of anesthesia. with emphasis on the application of the bispectral index and the middle latency auditory evoked response to the prevention of recall. *Anesthesiology* 2000; **93**· 876–82

2 Savoia G, Esposito C, Belfiore F, Amantea B, Cuocolo R. Propofol infusion and auditory evoked potentials. *Anaesthesia* 1988; **43** (Suppl): 46–9

3 Thornton C, Sharpe RM Evoked responses in anaesthesia. *Br J Anaesth* 1998; **81**: 771–81

4 Davies FW, Mantzaridis H, Kenny GN, Fisher AC Middle latency auditory evoked potentials during repeated transitions from consciousness to unconsciousness. *Anaesthesia* 1996, **51**: 107–13

5 Tooley MA, Greenslade GL, Prys-Roberts C Concentration-related effects of propofol on the auditory evoked response. *Br J Anaesth* 1996; **77**: 720–6

6 Schwender D, Kaiser A, Klasing S, Peter K, Poppel E. Midlatency auditory evoked potentials and explicit and implicit memory in patients undergoing cardiac surgery. *Anesthesiology* 1994; **80**· 493–501

7 Rundshagen I, Schnabel K, Schulte am Esch J. Median nerve evoked responses and explicit memory during recovery from isoflurane/nitrous oxide anesthesia. *Can J Anaesth* 2000; **47**: 494–502

8 Ozdamar O, Kraus N. Auditory middle-latency responses in humans. *Audiology* 1983; **22**: 34–49

9 Thornton C, Konieczko KM, Knight AB, *et al.* Effect of propofol on the auditory evoked response and oesophageal contractility. *Br J Anaesth* 1989; **63**: 411–7

10 Chassard D, Joubaud A, Colson A, *et al.* Auditory evoked potentials during propofol anaesthesia in man. *Br J Anaesth* 1989; **62**: 522–6

11 Thornton C, Konieczko K, Jones JG, *et al.* Effect of surgical stimulation on the auditory evoked response. *Br J Anaesth* 1988, **60**: 372–8

12 Crabb I, Thornton C, Konieczko KM, *et al.* Remifentanil reduces auditory and somatosensory evoked responses during isoflurane anaesthesia in a dose-dependent manner. *Br J Anaesth* 1996; **76**: 795–801

13 McPherson D, Starr E. Auditory evoked potentials in the clinic. In: Halliday AM, ed. *Evoked Potentials in Clinical Testing* Edinburgh: Churchill Livingstone, 1993, 359–81

14 Rundshagen I, Schnabel K, Schulte am Esch J. Midlatency median nerve evoked responses during recovery from propofol/sufentanil total intravenous anaesthesia. *Acta Anaesthesiol Scand* 2000; **44**: 313–20

15 Munglani R, Andrade J, Sapsford DJ, Baddeley A, Jones JG A measure of consciousness and memory during isoflurane administration· the coherent frequency. *Br J Anaesth* 1993; **71**. 633–41

16 Reinsel RA, Veselis RA, Wronski M, Marino P The P300 event-related potential during propofol sedation: a possible marker for amnesia? *Br J Anaesth* 1995; **74**: 674–80

17 Thornton C, Sharpe RM The auditory evoked responses and memory during anesthesia. In: Ghoneim MM, ed *Awareness during Anesthesia*. Oxford: Butterworth Heinemann, 2001; 117–28

18 Jensen EW, Nebot A, Caminal P, Henneberg SW. Identification of causal relations between haemodynamic variables, auditory evoked potentials and isoflurane by means of fuzzy logic *Br J Anaesth* 1999; **82**: 25–32

19 Mantzaridis H, Kenny GN Auditory evoked potential index· a quantitative measure of changes in auditory evoked potentials during general anaesthesia *Anaesthesia* 1997, **52**: 1030–6

20 White M, Schenkels MJ, Engbers FH, *et al.* Effect-site modelling of propofol using auditory evoked potentials. *Br J Anaesth* 1999, **82**: 333–9

21 Doi M, Gajraj RJ, Mantzaridis H, Kenny GN. Relationship between calculated blood concentration of propofol and electrophysiological variables during emergence from anaesthesia· comparison of bispectral index, spectral edge frequency, median frequency and auditory evoked potential index. *Br J Anaesth* 1997; **78**. 180–4

University College of
LIBRARY
Calcutta

British Journal of Anaesthesia 89 (3)· 382–8 (2002)

Effect of propofol anaesthesia on the event-related potential mismatch negativity and the auditory-evoked potential N1

T. P. Simpson[1], A. R. Manara[1]*, N. M. Kane[2], R. L. Barton[3], C. A. Rowlands[3] and S. R. Butler[3]

[1]Department of Anaesthesia and [2]Department of Neurophysiology Frenchay Hospital, Frenchay Park Road, Bristol BS16 1LE, UK. [3]The Burden Neurological Institute, Stoke Lane, Bristol BS16 1QT, UK

**Corresponding author*

Background. Studies on the effects of anaesthesia on event-related potentials and long latency auditory-evoked potentials (AEP) are sparse. Both provide information on cortical processing and may have potential as monitors of awareness. We studied the effect of propofol on the event-related potential mismatch negativity (MMN) and the long-latency AEP N1.

Methods. Twenty-one patients received 1 μg ml^{-1} stepped increases in the target concentration of propofol using Diprifusor™ until a maximum of 6 μg ml^{-1} was achieved or the patient had lost consciousness. Neurophysiological responses (MMN and N1) and the patients' level of consciousness were recorded before the administration of propofol and at a target effector site concentration of propofol of 1, 2, 3, 4, and 6 μg ml^{-1}. Grand average evoked potentials were computed at baseline, before the administration of propofol (A); at the highest propofol concentration at which each patient was responsive (B); and at the concentration of propofol at which the patient became unconscious (C).

Results. Patients lost consciousness at different target concentrations of propofol, all being unresponsive by 4 μg ml^{-1}. The response to the deviant stimuli used to elicit duration-shift MMN was significantly more negative than to the standard stimuli at A (mean difference 2.58 μV, P=0.0011) but this difference was virtually abolished at point B, before the patients lost consciousness (mean difference 0.63 μV, P=ns). The amplitude of N1 evoked by standard stimuli was negative compared with electrical baseline at both point A (mean amplitude –3.81 μV, P<0.001) and at point B (mean amplitude –2.2 μV, P=0.002), but was no longer significantly different to baseline at point C (mean amplitude 0.51 μV, P=ns). The change in the mean amplitude of N1 from last awake (point B) to first unconscious (point C) was also significant (mean difference in amplitude 1.69 μV, P=0.02).

Conclusions. MMN is unlikely to be a clinically useful tool to detect awareness in surgical patients. In contrast, the loss of N1 may identify the transition from consciousness to unconsciousness and deserves further study.

Br J Anaesth 2002; **89**: 382–8

Keywords: anaesthesia, depth, awareness; anaesthetics i.v., propofol; monitoring, depth of anaesthesia

Accepted for publication: March 14, 2002

As the sense of hearing has been reported to be the last to be lost and the first to be recovered during the induction of anaesthesia and the return of consciousness,[1] it is not surprising that the auditory-evoked potential (AEP) has been investigated as a potential monitor of the depth of anaesthesia. Most studies have concentrated on the middle latency (ML)AEP. The midlatency components are quantified in terms of their latency and amplitude or a ratiometric index.[2–5] The MLAEP are 'exogenous' evoked potentials components as their features are determined

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

mainly by the physical nature of the evoking stimulus. Therefore, whilst their presence establishes the integrity of the afferent auditory pathway they may not necessarily provide information on perceptual processing in the cerebral cortex or the capacity to lay down memory of the auditory experience, both of which would be important in a method for determining awareness during anaesthesia.

The long latency components (>80 ms) of the AEP (LLAEP) including P1, N1, P2, N2, and P3 are more sensitive to the psychological state of the subject. These 'endogenous' components are thought to reflect activity in areas of the cerebral cortex that are involved in the perceptual and cognitive processing of the auditory signal and have an established role in the study of human cognition.[6] They are best observed when a longer stimulus is used such as a tone burst of 80–100 ms duration. As they are generated by areas of cortex at and beyond the primary projection area, they may be better indicators of the effect of anaesthetic agents on mental state than MLAEP.

The N1 component of the LLAEP is not a single phenomenon but a summation of electrical activity from a number of anatomically and functionally discrete generators.[7] These can be distinguished in terms of their scalp distribution, their sensitivity to the physical properties of the stimulus (frequency and duration) and the subject's attention to it. However, subcomponents of the N1 potential are independent of attention[8] and this is clearly a prerequisite for a neurophysiological monitor of awareness.

Mismatch negativity (MMN) is an automatic response to changes in auditory input, generated primarily in auditory areas of the temporal cortex.[9] If a series of identical 'standard' tones is used to evoke N1, an infrequent 'deviant' tone (one differing in frequency, duration, loudness, or some other physical property from the 'standard') evokes an additional negative potential that overlaps and extends beyond the negativity of N1 itself. The response is almost unaffected by the subject's attention to the evoking stimulus. Näätänen and Lyytinen[10] postulated that MMN correlates with the laying down of echoic memory and that it serves to identify stimuli to which conscious attention should be directed. As it is not generated in the primary auditory cortex, but beyond in the auditory and probably frontal association cortex, it may identify the capacity of cerebral cortex to mediate mental activity. Indeed, the presence of MMN has been shown to be a sensitive predictor of the return of consciousness in patients with traumatic head injury.[11] There are no studies on the effects of anaesthesia on MMN. The presence of MMN may identify auditory awareness and the capacity to lay down auditory memories during anaesthesia.

The present study was, therefore, carried out to observe how N1 and MMN changed with a decreasing level of consciousness achieved by stepped increases in effector site concentration of propofol, and to determine if either measure had potential as a monitor of awareness during anaesthesia.

Patients and methods

We studied 21 ASA I or II unpremedicated patients aged between 31 and 65 yr who were to undergo elective general surgical procedures under general anaesthesia. The hospital ethics committee approved the study, and written informed consent was obtained from each patient. All subjects were free from neurological or otological disease. The study was carried out in the anaesthetic room before the start of the surgical procedure. The patients' arterial pressure, electrocardiogram, and peripheral oxygen saturation were monitored non-invasively. All patients received supplemental oxygen via a Hudson facemask at 4 litre min^{-1}.

The only drug administered for the duration of this study was propofol which was infused using a target-controlled infusion (TCI) system (Diprifusor™ TCI, Zeneca Ltd, Cheshire, UK).[12] The TCI system consists of a microprocessor-driven infusion pump that adjusts the infusion rate to achieve the desired target concentration of propofol as predicted by a three-compartment pharmacokinetic model.[13] The model assumes immediate mixing in blood and takes no account of the delay required to achieve drug equilibration in the brain. Thus, a delay occurs between the time the TCI system indicates that a target concentration has been achieved and the maximum pharmacodynamic effect. Using a computer simulation model of the pharmacokinetic variables, it was assumed that 5 min would be sufficient to achieve steady-state conditions between the blood and effector site compartments, and that after this period there would be minimal change in the clinical effect of the propofol.

After a baseline recording of the EEG and MMN had been made, the TCI pump was started and set to achieve a target blood concentration of 1 μg ml^{-1} and, after a period of 5 min for equilibration, EEG and MMN recordings were repeated. The level of consciousness was assessed at the end of the 5-min equilibration period and again after the recordings had been taken. The patients were deemed to be unconscious and unaware if they no longer obeyed commands and the eyelash reflex was absent. The procedure of infusion, equilibration, neurophysiological data collection, and assessment of consciousness was repeated at target blood concentrations of propofol of 2, 3, 4, and 6 μg ml^{-1}. The study was stopped if the mean arterial pressure was reduced by more than 20% of the baseline value. Only when all the required recordings had been made were further drugs administered and the airway manipulated to allow the planned surgical procedure to begin.

Neurophysiology

The EEG was recorded from 10 scalp electrodes (F3, Fz, F4, C3, C4; A1, A2, P3, P4, and Cz) referred to a nose electrode, with a time constant of 1.2 s and a high-frequency filter at 70 Hz. The recordings were subsequently referenced to averaged mastoids ((A1+A2)/2). The signals were amplified by a Nihon Koden 7300F EEG machine and digitized at 1000 Hz and 12-bit resolution. Responses to deviants and standards were averaged separately over epochs of 512 ms until responses to 32 deviants had been collected. Frequency-shift MMN was evoked using 990 Hz standard tones and 500 Hz deviants, each with a duration of 84 ms. Duration-shift MMN was evoked with 700 Hz tones, the standards lasting 75 ms and deviants 25 ms. Fifteen per cent of stimuli were deviants, 85% standards. All stimuli were presented at an intensity of 60 dB nl and with an inter-stimulus interval of 750 ms.

To observe the neurophysiological changes associated with the transition from consciousness to unconsciousness we calculated grand averages of the N1 and MMN responses (duration-shift and frequency-shift) in each patient at the following times:

1. A, baseline, before administration of propofol;
2. B, at the target concentration of propofol each patient was last conscious;
3. C, at the target concentration at which they were first unconscious.

Statistical methods

MMN corresponds to a period of greater negativity in the response to the deviant than the standard stimuli in the period following N1. To assess whether MMN was reliably present, the difference in the mean voltage of the responses to standards and deviants was assessed using paired Student's *t*-tests. The period for analysis was chosen by inspection of the grand average responses recorded before the administration of propofol, which is at stage A. This showed that frequency-shift MMN was present during the period 100–250 ms after the stimulus and 140–250 ms in the case of duration-shift MMN. The onset of duration-shift MMN is later than that of frequency-shift MMN because detection of the deviant cannot begin until the (longer) tone has ended.

To determine whether the amplitude of N1 itself differed significantly from electrical baseline, the mean voltage of the response to standards in the period 90–135 ms after the stimulus was assessed using paired Student's *t*-tests. The period was selected because it spans the peak of N1 in the grand average recorded before the administration of propofol.

Results

Propofol dose and level of consciousness

Patients lost consciousness at different target concentrations of propofol. Eight patients became unresponsive for the first time at 2 μg ml^{-1}, 11 at 3 μg ml^{-1}, and two at 4 μg ml^{-1}. In no patient was there a change in level of consciousness between the end of the equilibration period and the next increase in the dose of propofol. Thus, the target blood concentration of propofol did not accurately predict the point at which consciousness was lost.

MMN

The changes in duration-shift MMN recorded from electrode Fz with respect to mastoids at times A, B, and C are shown in Figure 1. In the baseline recording, before the administration of propofol, the response to the deviants was significantly more negative than that to standards (mean difference=2.58 μV; standard error (SE) of the difference 0.68 μV; P=0.0011). At the target concentration of propofol at which the subjects were last aware, duration-shift MMN was already virtually abolished, that is its amplitude was no longer significantly different from zero (0.63 μV; SE=0.64 μV; P=ns). Once the subjects became unconscious, the response to deviants became more positive than that to standards though the difference did not reach significance. The amplitude of the MMN when the subjects were last aware did not differ significantly from its amplitude when they were first unconscious (mean difference 2.1 μV; SE=1.11; P=ns).

Frequency-shift evoked a MMN, which, as expected, began slightly earlier than that to duration-shift. Figure 2 shows the MMN to frequency-shift recorded from electrode Fz with respect to mastoids at three levels of consciousness. In the baseline recording, the response to the deviants was significantly more negative than that to the standards (mean difference=2.31 μV; SE=0.73 μV; P=0.005). Frequency-shift evoked a MMN that was still present in the last recording made while the subjects were last conscious (mean difference=1.38 μV; SE=0.56 μV; P=0.02). The response to the deviants remained more negative than that to standards after loss of consciousness but the difference was no longer significant. The variance in the amplitude of the MMN increased considerably with the onset of unconsciousness. Although its amplitude was lower than when the subjects were last conscious, the difference between the two conditions was not significant (mean difference=0.84 μV; SE=3.11; P=ns).

N1

N1 is the peak in the response to the standard tones. For example, the 700 Hz 75 ms tones, used as standards to evoke the duration-shift MMN, evoke an N1 potential that has a latency of approximately 110 ms (Fig. 3). In the baseline recording, N1 had a mean amplitude of –3.81 μV (significantly above baseline: SE=0.54 μV; P<0.0001) in the latency window 90–135 ms. Figure 3 also shows a systematic decrease in the mean amplitude of N1 with increasing target blood concentrations of propofol. The amplitude of N1 was still negative with respect to baseline at 2 μg ml^{-1} (1.5 μV; SE=0.69 μV; P=0.044) but the trace became significantly more positive than baseline during the same period at 3 μg ml^{-1}.

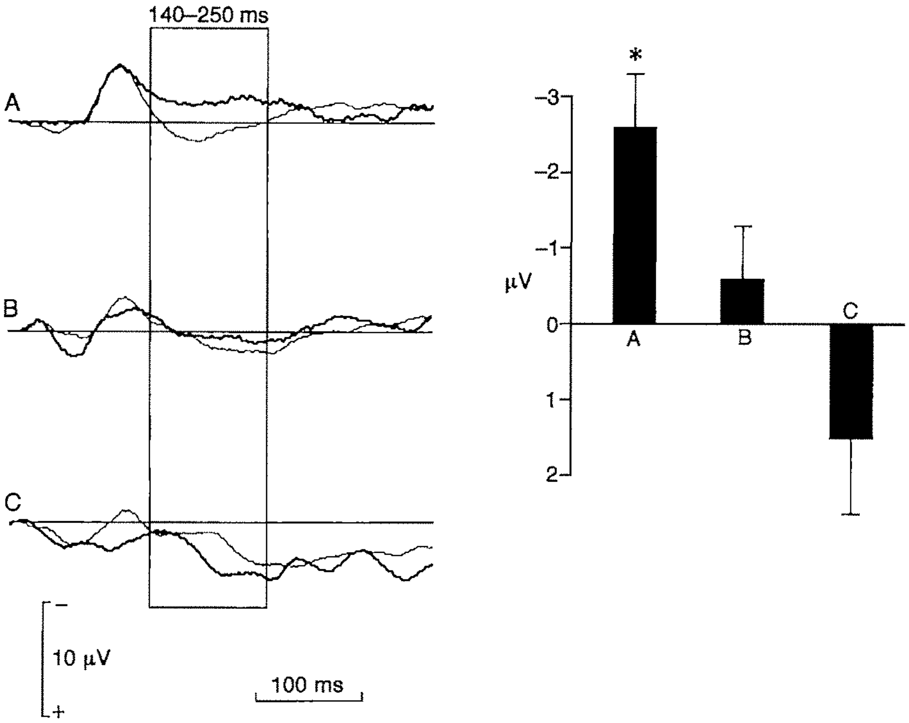


Fig 1 The mean amplitude of duration-shift MMN 140–250 ms after the stimuli at different levels of consciousness. (Left) Grand average waveforms The thin lines are responses to standard stimuli, thick lines responses to deviant stimuli (Right) Mean amplitude of MMN with SE A=at baseline, B=at the highest target concentration at which patients were last conscious, and C=at target concentration at which consciousness was first lost. *Responses to deviant stimuli significantly more negative than responses to standards.

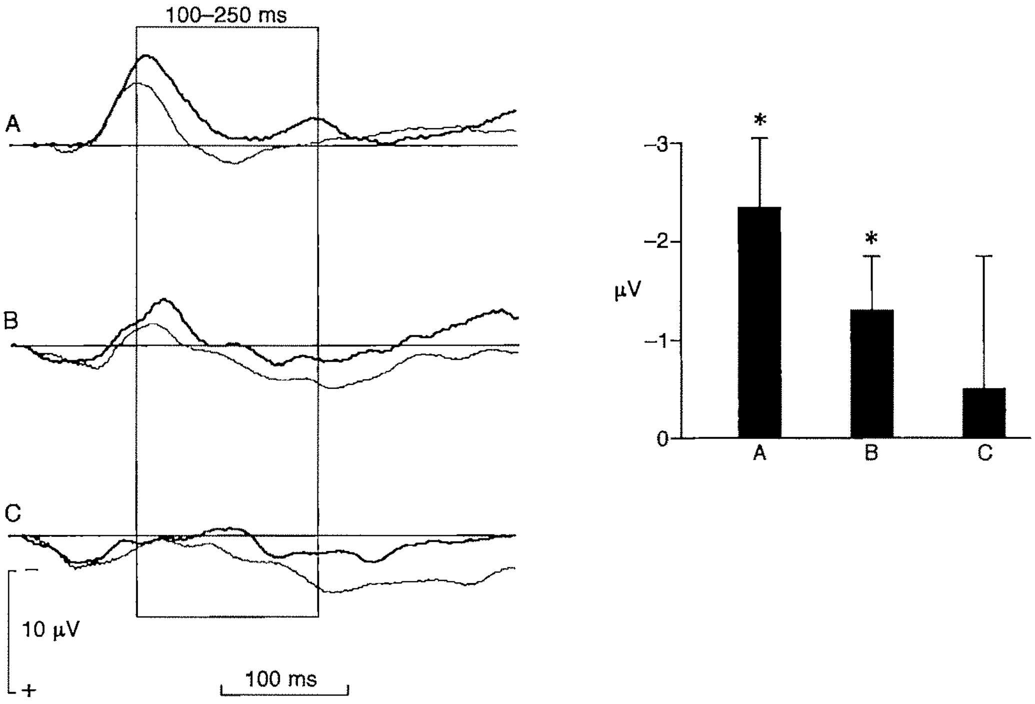


Fig 2 The mean amplitude of frequency-shift MMN 100–250 ms after the stimuli at different levels of consciousness Caption as Figure 1

The mean amplitude of N1 at the highest concentration of propofol at which subjects were still conscious fell to −2.2 µV (Fig. 4) but this remained significantly above the electrical baseline (SE=0.65 µV; P=0.002). Once subjects were unconscious, the mean amplitude dropped to −0.51 µV a value not significantly different from zero (SE=0.42 µV,

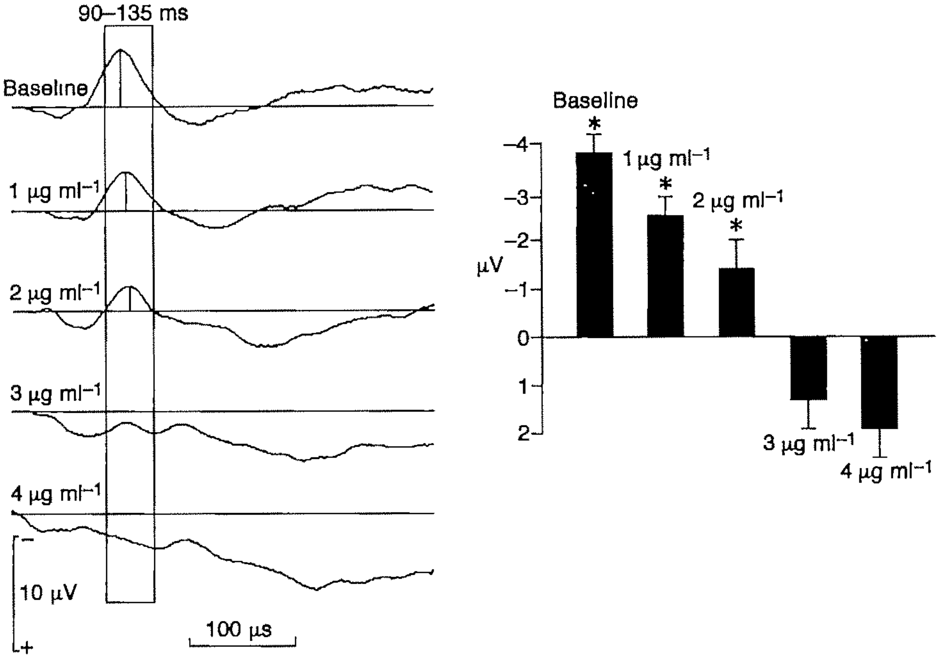


Fig 3 The mean amplitude of N1 90–135 ms after standard stimuli (75 ms duration 700 Hz), at increasing predicted blood concentrations of propofol. *Responses whose amplitudes are significantly different from the electrical baseline

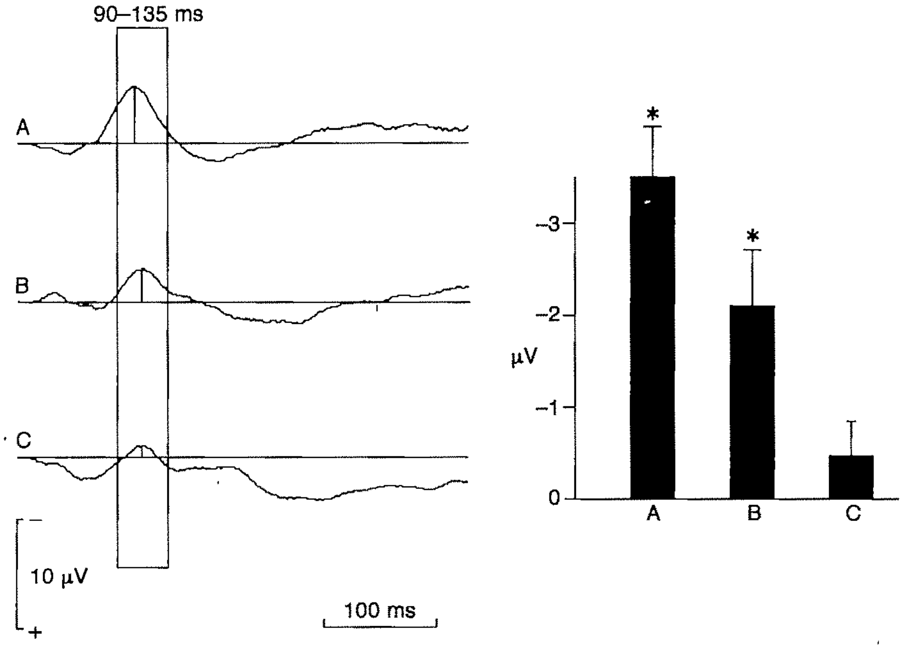


Fig 4 The amplitude of N1 90–135 ms after standard stimuli at different levels of consciousness. Caption as Figure 3

P=ns). The change in the mean amplitude of N1 from last awake to first unconscious was significant (mean difference 1.69 μV; SE=0.50 μV; P=0.02).

The N1, in response to the 900 Hz tones, used as standards to evoke the frequency-shift MMN showed similar changes in mean amplitude with the level of consciousness. The mean amplitude of N1 at baseline was −4.3 μV in the period between 90 and 135 ms after the stimulus. Although it was reduced to −1.8 μV at the concentration of propofol when patients were last conscious, this was still significantly different from zero (SE=0.52 μV; P=0.003). Once consciousness was lost, the mean amplitude of the signal in the 90–135 ms window became positive at +1.1 μV but not significantly different from zero (t=1.97, P=ns). The variance in the amplitude of N1 did not increase during the same period as it did for MMN. The change in N1 amplitude from last awake to unconsciousness was significant (mean difference=2.9 µV; SE=0.71 µV; P=0.001).

Discussion

In this study we showed that both duration-shift and frequency-shift MMN were abolished by concentrations of propofol insufficient to produce unconsciousness. There were several patients in whom a clear MMN could not be elicited despite them being conscious and obeying commands. The variability of the frequency-shift MMN waveform after loss of consciousness would make it difficult to determine if it is present or absent in individual patients. Though the variability of the waveforms was somewhat less in the response to duration-shift, the MMN evoked by this form of stimulation was abolished before consciousness was lost. MMN, as recorded in this investigation, does not appear to discriminate the level of consciousness as we hypothesized on the basis of its role in cognitive processing. No tests of implicit or explicit learning or memory were used in this study, but it has been repeatedly documented that patients who are lightly anaesthetized can obey commands yet have no explicit memory of the event.[14 15] If MMN is representative of short-term auditory echoic memory, then one could reasonably expect it to be present if explicit memory is being laid down. It is possible that the concentration of propofol at which MMN disappears is that at which the ability to lay down explicit or implicit auditory memory is lost, as opposed to that at which consciousness is lost. While the relationship between MMN and the formation of long-term memory has not been studied, the disappearance of MMN before loss of consciousness would be in accord with the dissociation between awareness and the ability to establish memories. Clearly this hypothesis would require further study.

The technical problems in recording MMN in individual patients also need to be addressed. Several factors contribute to the variability in the MMN responses. To evoke MMN it is necessary to use deviant stimuli that are, by definition, relatively infrequent. If recordings are to be clinically useful they must be made in the shortest possible time to enable changing levels of awareness to be detected. Almost 3 min were required to accumulate 32 epochs into the average response to deviants. An average containing so few responses may still be affected by noise induced from equipment in the theatre environment and the increases in amplitude of the background EEG as anaesthesia is induced. Increasing the number of responses to deviant stimuli would allow better resolution of the MMN response but at the cost of increasing the time required between recordings to a clinically unacceptable extent. Furthermore, since this study began, there have been preliminary reports of test–retest variation in serial recordings of MMN.[16 17] These indicate that MMN may occasionally be unrecordable even in awake, unanaesthetized subjects. Although the factors responsible for this have not been determined, the finding casts further doubt on the value of MMN as a monitor of depth of anaesthesia.

In contrast, N1 evoked by the standard stimuli was less vulnerable to these sources of variance because many more responses were included in the average (approximately 200). This component stayed significantly above baseline while the patients remained conscious with both the 990 Hz 84 ms (used to evoke frequency-shift MMN) and the 700 Hz 75 ms standard tone bursts (used for duration-shift MMN). Once consciousness was lost, the waveform evoked by the 700 Hz tones fell to baseline in the period occupied previously by the N1 and became positive in response to 900 Hz tones. This is in keeping with the findings of previous reports of the effect of anaesthesia on N1. However, in these studies the induction of anaesthesia was by a rapid bolus of i.v. anaesthetic agent and the transition period from consciousness to unconsciousness was not studied in detail.[18–20] In the present study, slowly increasing the depth of anaesthesia using the TCI system enabled us to see how N1 varied with predicted blood propofol concentration and the level of consciousness.

It may be argued that a longer period of equilibration than that chosen for this study is required to achieve a steady-state concentration of propofol at the effector site compartment.[21] Therefore, it is possible that the concentration of propofol may have continued to increase from the end of the equilibration period to the end of data collection and may have had some effect on the neurophysiological variables being measured. While this is possible, the effects on our results should be minimal for two reasons. First, as we were using only 3- to 4-min epochs of data and the sequence of recordings was the same at each concentration of propofol, then the effect should have been consistent on each of the variables measured. Secondly, and more importantly, there was no change in the level of consciousness between the end of the equilibration period and the end of data collection in any patient. The study was primarily concerned with neurophysiological changes occurring at the transition from consciousness to unconsciousness, and not the correlation of neurophysiological variables to the predicted plasma concentration of anaesthetic agent. However, in the light of our findings it would be prudent if in future studies the time period for equilibration were increased and the incremental increase in the target concentration of propofol reduced to 0.2 or 0.5 µg ml^{-1} increments, particularly in the range where consciousness is lost, that is 2–4 µg ml^{-1}.

The mean amplitude of N1 was a more sensitive predictor of the transition from consciousness to unconsciousness than was the predicted blood concentration of propofol. This is not surprising given the inter-individual pharmacokinetic and haemodynamic variability that will markedly affect each patient's response to propofol and the fact that the

Diprifusor™ system has been shown to have a median performance error of 16%, even if allowed to equilibrate.[22] The later part of these waveforms becomes increasingly positive with reducing levels of consciousness. This phenomenon can be observed in the recordings of long latency event-related potentials published by previous investigators.[20 23] Although the waveforms are different from those which occur during normal consciousness, they indicate that some form of stimulus-related activity is still taking place in the cerebral cortex at these levels of anaesthesia. We hope to investigate the reproducibility and significance of this phenomenon in future studies.

Our study may be criticized for studying mean values as opposed to individual patient data. The study was designed to investigate the effect of loss of consciousness on the selected neurophysiological variables recorded and to that end multiple variables were studied for short periods only and grand averages compared. As we believe that in N1 we have identified a possibly useful neurophysiological marker of the transition from consciousness to unconsciousness, future studies of this variable should collect data over longer periods and compare changes in individual patients.

In conclusion, we have shown that the event-related potential MMN is not a robust measure of loss of consciousness and have postulated that it may represent the loss of ability to lay down auditory memory. We also demonstrated that the disappearance of the LLAEP N1 identifies the transition from consciousness to unconsciousness and warrants further investigation of its suitability of a monitor of depth of anaesthesia.

Acknowledgements

This research was supported by The Burden Trust and by BIOMED-2 contract BMH4-CT96-0819-COBRAIN of the European Union Part of this work was presented at the 4th International Symposium on Memory and Awareness in Anaesthesia, Northwick Park, June 1998 and has been published in the proceedings of that meeting.

References

1 Jones JG, Konieczko K. Hearing and memory in anaesthetised patients. *Br Med J* 1986; **292**: 1291–2

2 Thornton C, Barrowcliffe MP, Konieczko KM, Ventham P, Dore CJ, Newton DE. The auditory evoked response as an indicator of awareness. *Br J Anaesth* 1989; **63**: 113–5

3 Thornton C, Sharpe RM. Evoked responses in anaesthesia. *Br J Anaesth* 1998; **81**: 771–81

4 Schwender D, Daunderer M, Mulzer S, Klasing S, Finsterer U, Peter K. Midlatency auditory evoked potentials predict movements during anesthesia with isoflurane or propofol. *Anesth Analg* 1997; **85**: 164–73

5 Doi M, Gajraj RJ, Mantzaridis H, Kenny GN. Relationship between calculated blood concentration of propofol and electrophysiological variables during emergence from anaesthesia: comparison of bispectral index, spectral edge frequency, median frequency and auditory evoked potential index. *Br J Anaesth* 1997; **78**: 180–4

6 Hillyard SA, Kutas M. Electrophysiology of cognitive processing. *Annu Rev Psychol* 1983; **34**: 33–61

7 Naatanen R, Picton TW. The N1 wave of the human electricand magnetic response to sound: a review and analysis of the component structure. *Psychophysiology* 1987; **24**· 375–425

8 Winter O, Kok A, Kenemans JL, Elton M. Auditory event related potentials to deviant stimuli during drowsiness and stage 2 sleep. *Electroencephalogr Clin Neurophysiol* 1995; **96**: 398–412

9 Naatanen R. The mismatch negativity: a powerful tool for cognitive neuroscience. *Ear Hearing* 1995; **16**: 6–18

10 Nàätanen R, Lyytinen H. Mismatch negativity in sleep. In: Ogilvie RD, Harsh JR, eds *Sleep Onset, Normal and Abnormal Processes*. Washington: American Psychological Association, 1995; 339–49

11 Kane NM, Curry SH, Rowlands CA, Cummins B, Manara AR, Butler SR. Event related potentials—neurophysiological tools for predicting emergence and early outcome from traumatic coma. *Intensive Care Med* 1996; **22**. 39–46

12 Kenny GNC, White M. A portable target controlled propofol infusion system. *Int J Clin Monit Comput* 1992; **9**: 179–82

13 Marsh B, White M, Morton N, Kenny GNC. Pharmacokinetic model driven infusion of propofol in children. *Br J Anaesth* 1991; **67**: 41–48

14 Andrade J, Munglani R, Jones JG, Baddeley AD. Cognitive performance during anaesthesia. *Consciousn Cogn* 1994; **3**: 148–65

15 Ghoneim MM, Block RI, Dhanaraj VJ. Interaction of a subanaesthetic concentration of isoflurane with midazolam. effects on responsiveness, learning and memory. *Br J Anaesth* 1998; **80**: 581–7

16 Morlet D, Bertrand O, Giard MH, Bouchet P, Fischer C Long-lasting continuous monitoring of MMN. In: *Abstracts of the First International Workshop on Mismatch Negativity and it Clinical Applications*. Helsinki: University of Helsinki, Mulktiprint 1998; 30

17 Morlet D, Fischer C. MMN System for coma monitoring: development and parameter optimisation. In: *Summary of the Fourth COBRAIN Meeting—Progress Report to the European Commission Biomed 2 Programme*. 1997; 20

18 Plourde G, Joffe D, Villemure C, Trahan M. The P3a wave of the auditory event-related potential reveals registration of pitch change during sufentanil anesthesia for cardiac surgery. *Anesthesiology* 1993; **78**: 498–509

19 Plourde G, Picton TW. Long-latency auditory evoked potentials during general anesthesia: N1 and P3 components. *Anesth Analg* 1991; **72**: 342–50

20 vanHooff JC, de Beer NA, Brunia CH, Cluitmans PJ, Korsten HH. Event-related potential measures of information processing during general anaesthesia. *Electroencephalogr Clin Neurophysiol* 1997; **103**: 268–81

21 White M, Schenkels MJ, Engbers FHM, *et al.* Effect-site modelling of propofol using auditory evoked potentials. *Br J Anaesth* 1999; **82**: 333–9

22 Swinhoe CF, Peacock JE, Glen JB, Reilly CS. Evaluation of the predictive performance of a 'Diprifusor' TCI system. *Anaesthesia* 1998; **53**: 61–7

23 de Beer NA, van Hooff JC, Brunia CH, Cluitmans PJ, Korsten HH, Beneken JE. Midlatency auditory evoked potentials as indicators of perceptual processing during general anaesthesia. *Br J Anaesth* 1996; **77**: 617–24

British Journal of Anaesthesia 89 (3): 389–97 (2002)

Prediction of the haemodynamic response to tracheal intubation: comparison of laser-Doppler skin vasomotor reflex and pulse wave reflex

M. Luginbühl[1]*, F. Reichlin[2], G. H. Sigurdsson[4], A. M. Zbinden[3] and S. Petersen-Felix[1]

[1]Staff Anaesthesiologist, Department of Anaesthesiology University Hospital of Bern, CH-3010 Bern, Switzerland. [2]Department of Anaesthesiology, Kantonsspital Münsterlingen, Switzerland. [3]Research Section, Department of Anaesthesiology University Hospital of Bern, Switzerland. [4]Department of Anaesthesiology and Intensive Care, University Hospital Reykjavik, Iceland

**Corresponding author*

Background. The laser-Doppler skin vasomotor reflex (SVmR) caused by tetanic stimulation of the ulnar nerve may be a test that can predict the haemodynamic response to tracheal intubation. A decrease in pulse wave amplitude (pulse wave reflex, PWR) may be an alternative index of this response. We compared the abilities of PWR and SVmR to predict the haemodynamic response to tracheal intubation and studied how alfentanil, muscle relaxation, stimulation site and stimulation pattern affected the two reflexes.

Methods. Anaesthesia was induced and maintained with 2% sevoflurane and 50% nitrous oxide in two groups of 10 ASA status I patients. Tetanic stimuli were applied to the flexor muscles of the forearm and the ulnar nerve before and after administration of vecuronium. The change in skin blood flow (laser-Doppler) and pulse wave amplitude (pulse oximetry) after a 5 and 10 s stimulation was measured on the opposite hand. If skin blood flow (laser-Doppler) decreased by more than 10%, a computer-controlled infusion of alfentanil was started and the target plasma concentration was increased in steps until this response was suppressed (<10%). The trachea was intubated and arterial pressure and heart rate responses were recorded. Plasma alfentanil concentration was measured.

Results. When PWR and SVmR were suppressed, the haemodynamic response to tracheal intubation was reduced in 100 and 53% of patients respectively. PWR and SVmR responses decreased with increasing plasma alfentanil concentration. The SVmR response to muscle stimulation was reduced by muscle relaxants. The pulse wave response to both muscle and neural stimulation was reduced by relaxants. The responses to 5 and 10 s stimulations were similar.

Conclusion. An absent SVmR does not predict a blunted arterial pressure or heart rate response to tracheal intubation. The PWR may be a better predictor.

Br J Anaesth 2002: **89**: 389–97

Keywords: intubation, tracheal; measurement techniques, laser-Doppler flowmetry; measurement techniques, pulse wave amplitude; pain, experimental

Accepted for publication: April 16, 2002

Changes in arterial pressure or heart rate caused by painful stimulation may be harmful in patients with cardiovascular disease.[1] Tracheal intubation is a powerful noxious stimulus. A 50% greater anaesthetic concentration is needed to suppress movement after intubation than after skin incision.[2–4] The minimal alveolar concentration required to suppress the haemodynamic response to skin incision (MAC bar) is 1.3 times MAC.[5] Variation in anaesthetic drug requirement between patients means that haemodynamic responses to tracheal intubation and skin incision may be insufficiently reduced. A small painful stimulus and an appropriate method of assessing the response to this stimulus would be useful for assessing the haemodynamic reactivity of an individual patient to a greater stimulus.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Shimoda and co-workers[6] suggested that cutaneous vasoconstriction after electrical tetanic stimulation of the ulnar nerve (skin vasomotor reflex, SVmR) could predict the arterial pressure response to tracheal intubation. After suppressing the skin vasomotor reflex with sevoflurane, they observed a much reduced arterial pressure response to tracheal intubation.[6] They used a 3 s, 40 mA, 50 Hz electrical stimulation of the ulnar nerve,[6] which was different from the stimulus used by Zbinden and co-workers (10 s, 60 mA, 50 Hz to the forearm muscles).[2] The effect of opioids and neuromuscular blockade on these responses was not assessed and the responses to muscle and neural stimulation were not compared.

Measurement of skin blood flow with laser-Doppler flowmetry is expensive and not used routinely in clinical practice. The amplitude of the pulse oximeter wave could be an alternative index of vascular tone[7] and correlates with the laser-Doppler signal.[8] We considered the possibility that measurement of pulse oximeter amplitude, which is widely available, might be as useful as the laser-Doppler method to indicate vasoconstriction. We measured the pulse wave reflex (PWR) as the minimal pulse wave amplitude after a painful stimulus divided by the mean pulse wave amplitude before the stimulus.

We set out to confirm that SVmR could predict a reduced haemodynamic response to tracheal intubation. We used an opioid instead of sevoflurane and assessed the PWR as a predictor of the haemodynamic response to intubation. We also assessed the effect of plasma alfentanil concentration and compared the effects of muscle relaxation and the effects of muscle and ulnar nerve stimulation on the two reflex responses.

Patients and methods

Patients

After approval by the local ethics committee and after written informed consent, we studied two groups of 10 ASA physical status I patients having elective surgery under general anaesthesia. We excluded patients who could not give informed consent, those receiving treatment that could affect MAC (e.g. sedative or tricyclic antidepressant drugs) and patients with a difficult airway.

Study plan

Patients were given omeprazole 40 mg (Antra®; AstraZeneca, Zug, Switzerland) on the evening before the study. In the operating theatre, standard monitoring devices were applied (Datex AS3 Compact, Datex-Ohmeda; Instrumentarium Corporation, Helsinki, Finland), a venous cannula was inserted in the non-dominant arm, and patency of the ulnar artery of both arms was assessed with Allen's test. On the non-dominant hand, an angled laser-Doppler flowmeter probe (PF 404; Perimed, Järfälla, Sweden) was placed on the fourth finger, a pulse-oximeter probe on the third finger and a skin temperature probe on the palm. The patient was then covered with a warming blanket (Bair Hugger; Augustine Medical, MN, USA). When the laser-Doppler signal was stable, the patients were asked to perform a brisk inspiration (inspiratory gasp), which should cause a short-lasting skin vasoconstriction.[9] Patients without this reaction were excluded from the study as this indicates abnormal vasomotor function.[9]

First study

Anaesthesia was induced in the first group of 10 patients by vital capacity inhalation of 7 vol% sevoflurane in nitrous oxide/oxygen (ratio 1:1), and the end-tidal sevoflurane and nitrous oxide concentrations were kept at 2 and 50 vol% respectively. The patients were ventilated by facemask and the end-tidal carbon dioxide concentration was maintained between 35 and 45 mm Hg throughout the study. A 20-G radial arterial cannula was inserted in the non-dominant arm. A temperature probe was placed in the rectum.

Skin electrodes for electrical stimulation were placed along a line between a point 1 cm ulnar to the mid-point of the cubital fold (point A) and a point 1.5 cm ulnar to the mid-point of the first wrist fold (point B). The muscle electrodes were attached 5 and 13 cm distal to A[2] and the ulnar nerve electrodes 15 and 23 cm distal to A.[6] A 5 s, 60 mA, 50 Hz, 0.25 ms square-wave electrical stimulus[10] was applied by a Digitimer DS 7 constant current stimulator with a Digitimer DG2 trigger generator (Digitimer, Welwyn Garden City, Hertfordshire, UK) and a timer device (constructed in our laboratory). The positive pole of the stimulator was attached proximally. The tetanic stimulation was always applied first to the muscles and then to the ulnar nerve. After 10 min of equilibration, the first tetanic stimulation was applied. The second stimulation followed 3–5 min after vecuronium 0.1 mg kg^{-1} i.v., when at least three of the four twitches of the train-of-four were suppressed. Muscle relaxation was maintained at this level by further doses of vecuronium (0.02 mg i.v.) until the study was completed. If a positive laser-Doppler skin vasomotor reflex SVmR was present on ulnar nerve stimulation, an infusion of alfentanil was started to give a target plasma concentration of 25 ng ml^{-1}. A Harvard 22 infusion pump (Harvard Apparatus, South Natick, MA, USA) was controlled by an IBM-compatible laptop computer running the Stanpump program (S. L. Shafer, Anesthesiology Service (112A), PAVAMC, Palo Alto, CA, USA) using pharmacokinetic parameters for alfentanil.[11] After each positive SVmR, the alfentanil target concentration was increased by 25 ng ml^{-1} and the stimulations were repeated. As soon as the laser-Doppler SVmR was negative (for definition see below), tracheal intubation was performed by an experienced anaesthetist. The haemodynamic response to tracheal intubation was determined off-line from the heart rate computed from the ECG and the arterial pressure values (Datex AS3 compact, Datex-Ohmeda) recorded on a personal computer every 10 s (Labview version 5.0; National Instruments Corporation, Austin, TX, USA). An arterial pressure increase of more than 25 mm Hg and a heart rate increase of more than 25 beats min^{-1} were considered relevant. The mean arterial pressure and heart rate in the 120 s before intubation were used as reference. The duration of the procedure from the insertion of the laryngoscope to the inflation of the cuff and the view of the vocal cords according to Cormack and Lehane[12] were recorded.

Before each stimulation and before intubation, arterial blood samples were taken to measure plasma alfentanil concentration. Arterial blood gas measurements were made before the first tetanic stimulation and before intubation. Ten minutes after tracheal intubation, data acquisition was stopped and anaesthesia continued according to clinical routine.

Second study

The second group of 10 patients took part in this study. A 10 s, 60 mA, 50 Hz, 0.25 ms square-wave electrical impulse was used. The target concentration of alfentanil was initially 50 ng ml^{-1} and was increased in steps of 50 ng ml^{-1}. In all other aspects the plan was as in the first study.

Laser-Doppler SVmR

Blood flow in the finger was measured continuously with a laser-Doppler flow system (Periflux 4001; Perimed). The time constant of the flowmeter output amplifier was set to 0.02 s. The raw signal of the laser-Doppler was digitized at 128 Hz (A/D conversion card; National Instruments Corporation) and stored on a computer, and was also displayed during the study (arbitrary perfusion units according to the manufacturer's specifications). The laser-Doppler system was calibrated with a standard suspension of 2 mm latex spheres provided by the manufacturer (Perimed).

The mean laser-Doppler flow (perfusion units) was calculated at intervals of 1 s from the digitized raw signal. The skin vasomotor reflex amplitude (SVmR) was defined according to the equation

$$\mathrm{SVmR}=1-(b/a) \qquad (1)$$

where a is the mean laser-Doppler flow during the 120 s before stimulation and b is the minimal laser-Doppler flow after stimulation plus the standard deviation of a. The reflex was calculated for every stimulation according to the monitor readings and was considered absent if SVmR was 0.1 or less (i.e. the blood flow decreased by 10% or less; modified from Shimoda and colleagues).[6]

Pulse wave reflex

The pulse wave of the pulse oximeter (Datex AS3 Compact, Datex-Ohmeda) was scaled in arbitrary units from −100 to +100 and digitized at 128 Hz, like the laser-Doppler signal. The beat-to-beat amplitude of the pulse wave was measured off-line using software developed in our laboratory. The PWR was computed in the same way using equation (1), with the laser-Doppler flow replaced by the pulse wave amplitude.

Alfentanil plasma concentrations and performance of the target-controlled infusion

Blood samples for alfentanil measurement were immediately centrifuged at 3500 *g* for 30 min and the plasma was stored at −26°C. Alfentanil plasma concentration was measured by gas chromatography–mass spectrometry[13] with a detection limit of 0.04 ng ml^{-1}. We found coefficients of variation of 2.2, 2.5 and 4.7% at concentrations of 200, 50 and 5 ng ml^{-1} respectively for measurements made on the same day. Between days we found coefficients of variation of 4.2, 6.8 and 7.5% respectively. Fentanyl was used as internal standard.

Data analysis and statistics

The characteristics of the two groups were compared using Fisher's exact test and the Wilcoxon rank test as appropriate. Values are given as medians (first and third quartiles) or as mean (SD) if normally distributed.

Anaesthetic drug concentrations

From the measured alfentanil plasma concentrations of each subject, the prediction error of the pharmacokinetic model was calculated:

$$PE = \frac{C_m - C_p}{C_p} \times 100 \qquad (2)$$

where C_m is the measured concentration and C_p is the predicted plasma alfentanil concentration. The median prediction error (MDPE; a measure of bias) and the median absolute prediction error (MDAPE=median |PE|; a measure of accuracy) were computed for each individual.[14] Subsequently, the means of the MDPE (MDPE) and the MDAPE (MDAPE) were calculated for the groups.

The mean end-tidal sevoflurane and nitrous oxide concentrations for the period from 60 s before to 60 s after each stimulation were determined for each subject. Subsequently, the mean coefficients of variation of the sevoflurane and nitrous oxide concentrations were determined for the study population.

Prediction of response to tracheal intubation

The responses to the last ulnar nerve stimulation before tracheal intubation were analysed to estimate the probability of reduced arterial pressure and heart rate response to tracheal intubation if the laser-Doppler SVmR and the PWR were absent, i.e. the negative predictive value of these tests.

Effect of stimulation pattern on the reflex responses

The responses to stimulation before alfentanil administration in the first and second studies were compared (Mann–Whitney rank sum test) to detect a difference between the 5 and 10 s stimulations, considering muscle and ulnar nerve stimulation separately. As there was no difference between these responses, the results of the two studies were pooled for further analysis.

Effect of plasma alfentanil concentration on the reflex responses

The data were fitted to a non-linear regression model relating the laser-Doppler SVmR and PWR values to the corresponding measured plasma alfentanil concentrations according to the equation

$$y=y_0\times e^{-a\times x} \qquad (3)$$

where y is the reflex (either PWR or SVmR) at plasma alfentanil concentration x, y_0 is the reflex at zero alfentanil and a is the regression coefficient. The inter-individual variation of the estimated parameters (y_0 and a) was modelled with an additive error model.

$$P_i=P_{TV}+\eta_i \qquad (4)$$

where P_i is the parameter of the ith individual, P_{TV} is the typical parameter value of the population, and η_i is the random inter-individual variation of the parameter (with mean 0 and variance ω^2).

The residual error of the predicted effect including intra-individual variation[15] was also assumed to be additive:

$$E_{ij}=E_{TVi}+\varepsilon_{ij} \qquad (5)$$

where E_{ij} is the effect in the ith individual at the jth measurement, E_{TVi} the typical effect value for the ith individual and ε_j the residual variation of the effect at the jth measurement (with mean 0 and variance σ^2).

This non-linear mixed-effects model was implemented in Fortran pseudocode for use with the non-linear mixed-effects modelling program NONMEM.[16] The NONMEM objective function was minus twice the logarithm of the likelihood (–2LL). The objective function was minimized to obtain the best estimation of the parameters of the structural model, y_0 and a, and the related parameters of the error models, η and ε. The two parameters of the structural model were considered significant if the 95% confidence interval of the estimates did not include zero. The significance of each of the structural and error parameters was tested with the likelihood ratio test. A difference in the minimal value of the objective function between the reduced and the full model exceeding 3.841 was considered significant ($P<0.05$). If the minimal value of the objective function did not differ significantly between the full and the reduced model, a parameter was eliminated from the model.

Effect of muscle relaxation and stimulation site on the reflex responses

A signed rank test was used to test for differences between neural and muscle stimulation (using the responses to stimuli before neuromuscular block) and to compare the responses to neural and muscle stimuli before and after injection of the muscle relaxant.

The statistical analysis, except for NONMEM, was performed with Sigmastat version 2.0 (Jandel Scientific Corporation, San Rafael, CA, USA). $P<0.05$ was taken as significant.

Results

Patients

Ten ASA I patients were enrolled in each of the two studies. The characteristics of the patients are summarized in Table 1. Except for a slight but significantly greater age of the patients in the second study, the two groups of patients were similar. All patients had a vasoconstriction response to inspiration. After induction of anaesthesia with sevoflurane, there was an increase in laser-Doppler flow (median (first and third quartiles)) in the finger from 34 (24, 96) to 193

Table 1 Characteristics of the study population *Laryngoscopy grading according to Cormack and Lehane [12] No patient had a Mallampati or laryngoscopy score of more than 2. Type of surgery other than ENT. †orthopaedic, ‡abdominal

	Study 1 (5 s stimulation) (n=10)	**Study 2 (10 s stimulation) (n=10)**
Gender (male/female)	6/4	7/3
Age (yr) mean (range)	25 (20–37)	33 (21–51)
Weight (kg) mean (SD)	72 (11)	73 (12)
Height (cm) mean (SD)	174 (8)	172 (8)
Mallampati score 1, 2	8, 2	5, 5
Laryngoscopy score 1, 2*	4, 6	8, 2
Duration of intubation (s): mean (SD)	16.0 (4.1)	16.8 (5.7)
Type of surgery ENT, other	8, 2†	8, 2‡
Arterial $P\text{CO}_2$ (mm Hg): mean (SD)	42 (5)	40 (9)
Body temperature (°C): mean (SD)	36.6 (0.7)	36.6 (0.27)
Skin temperature at stimulation (°C): mean (SD)	36.0 (0.7)	35.7 (0.8)

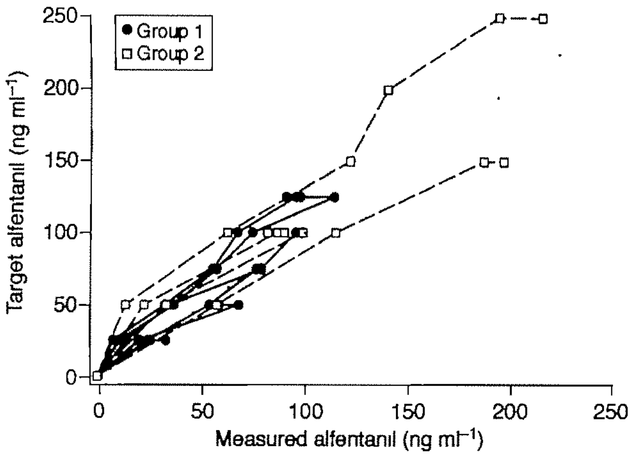


Fig 1 Measured and target plasma alfentanil concentrations at times of stimulation. The solid lines represent the subjects of study 1, with one filled circle for each pair of stimuli (nerve and muscle) The dashed lines represent the subjects of study 2, with one open square for each pair of stimuli. The last filled circle or open square of each line represents tracheal intubation. The dotted line is the line of equality.

(157, 245) perfusion units and in pulse wave amplitude (arbitrary units) from 2.0 (1.5, 2.6) to 8.5 (4.6, 10.1) (signed rank test, $P<0.001$). Finger temperature (mean (SD)) increased from 34.9 (1.8)°C at the start to 36.2 (0.9)°C at the end of the study procedure (signed rank test, $P<0.001$).

Anaesthetic drug concentrations

After equilibration, the end-tidal concentrations of nitrous oxide and sevoflurane were 49.02 (1.87) and 1.99 (0.07) vol% respectively. The mean (range) coefficients of variation of the end-tidal concentration of nitrous oxide and sevoflurane were 2 (0.2–7) and 0.5 (0.1–5)% respectively.

The MDPE, representing the bias of the alfentanil target-controlled infusion, and the MDAPE, representing its accuracy, were 7.6 and 17.7% respectively. Thus, the capacity of the selected pharmacokinetic parameters to predict plasma concentrations in our study population was comparable to that in a previous study (Fig. 1).[11]

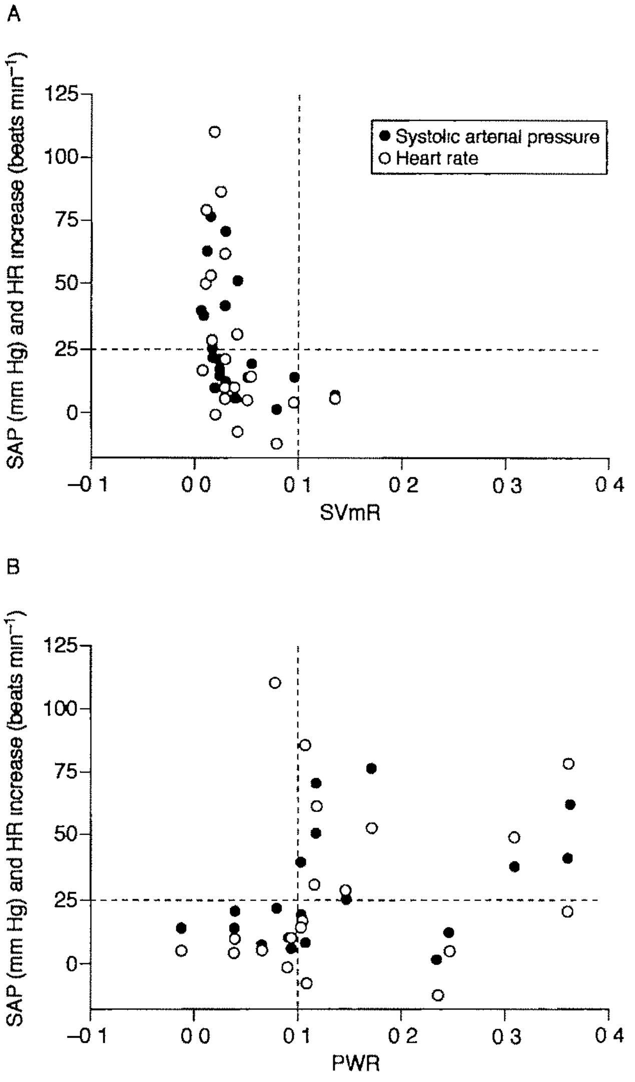


Fig 2 (A) The laser-Doppler skin vasomotor reflex (SVmR) and (B) the pulse wave reflex (PWR) related to the responses of systolic arterial pressure and heart rate to tracheal intubation For SVmR and PWR a value below 0.1 was defined as no response (vertical dotted line) A systolic arterial pressure or heart rate increase at intubation was considered relevant if greater than 25 mm Hg or 25 beats min^{-1} respectively (horizontal dotted line)

Prediction of the haemodynamic reaction to tracheal intubation by PWR and SVmR

The PWR before intubation was suppressed in seven of the 20 patients, whereas the laser-Doppler SVmR was suppressed in 19 of the 20 patients. One patient was intubated even though the SVmR remained positive at an alfentanil target concentration of 250 ng ml^{-1} as further prolongation of anaesthesia for the study was not appropriate. In the nine patients with a negative laser-Doppler SVmR but a positive PWR, the systolic arterial pressure is increased by more than 25 mmHg and the heart rate by more than 25 beats min^{-1} after tracheal intubation. Three of these were in the first and six in the second group of patients. This corresponds to a negative predictive value of 53% for laser-Doppler SVmR and 100% for the PWR (Fig. 2). The positive predictive value of the PWR was 69%.

In seven of the nine patients with a false-negative SVmR, the SVmR was already negative before the alfentanil infusion was started. Intubation was therefore done with 50 vol% nitrous oxide and 2 vol% sevoflurane. In the remaining two subjects a response occurred when the measured plasma alfentanil concentration was 98 and 81 ng ml^{-1} respectively. Only one patient with an absent laser-Doppler SVmR during inhalation anaesthesia (2 vol% sevoflurane and 50 vol% nitrous oxide) had no response to intubation.

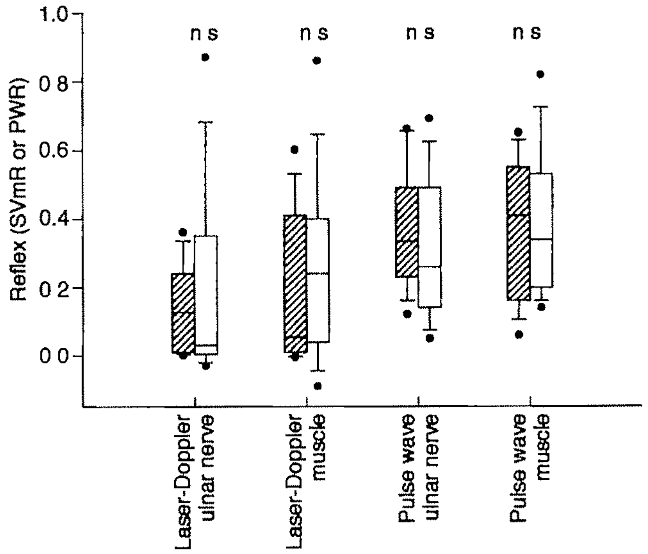


Fig 3 Laser-Doppler skin vasomotor reflex (SVmR) and pulse wave reflex (PWR) induced after tetanic stimulation of the ulnar nerve and of the flexor muscles of the forearm, before neuromuscular blockade and without opioids. The shaded bars represent 5 s stimuli and the open bars 10 s stimuli. Error bars represent 10th and 90th percentiles and points represent the 5th and the 95th percentiles.

Effects of stimulus pattern, alfentanil concentration, muscle relaxation and site of stimulation

The SVmR and PWR responses after 5 and 10 s stimuli given before alfentanil were similar (Fig. 3). The systolic arterial pressure increases after 5 and 10 s stimuli were 13.3 (6.6) mm Hg (range 0–23) and 19.2 (12.1) mm Hg (range 5.2–39) respectively (not significant).

The non-linear mixed effects model indicated a significant exponential decrease in both SVmR and PWR with increasing plasma alfentanil concentration (Fig. 4). The alfentanil effect was significant with ulnar nerve stimulation for both SVmR and PWR, whereas with muscle stimulation it was only significant for PWR. There was no significant difference between the slope parameters of PWR with ulnar nerve and muscle stimulation. The inter-individual error parameter η_{y0} of the baseline reflex (y_0) (equation (4)) showed considerable inter-individual variability, but the error parameter η_a of the regression coefficient a did not. The parameter η_a therefore did not improve the fit and was excluded from the final model (Table 2).

Vecuronium (0.1 mg kg^{-1}) reduced the laser-Doppler SVmR with direct muscle stimulation but not ulnar nerve stimulation, whereas the PWR was attenuated regardless of the stimulation site (Fig. 5). Neuromuscular blockade reduced the PWR after muscle stimulation more than after ulnar nerve stimulation (P=0.04).

Muscle or ulnar nerve stimulation of either duration given before administration of neuromuscular blocking drugs induced a similar SVmR and PWR (Fig. 5). After administration of vecuronium, however, the SVmR was significantly less after muscle than after ulnar nerve stimulation, whereas PWR remained similar after stimulation at either site.

Discussion

In contrast to a previous study,[6] we found that the laser-Doppler SVmR does not reliably predict a relevant haemodynamic response to intubation. However, the PWR after electrical stimulation of the ulnar nerve predicted a haemodynamic response more reliably. Neuromuscular block attenuated but did not suppress the PWR after both muscle and ulnar nerve stimulation, whereas it attenuated the laser-Doppler SVmR after muscle stimulation.

A test of analgesia in the anaesthetized patient may help prevent unexpected haemodynamic reactions to severe stimuli. It would supplement anaesthetic depth monitors, such as the bispectral index and auditory evoked potential monitors,[17 18] which indicate the hypnotic state. Although both SVmR and PWR were suppressed by alfentanil, the prediction of no response to tracheal intubation was poor with SVmR and good with PWR. The PWR, which could be easily measured clinically, could be a good alternative to the expensive and rarely available laser-Doppler (SVmR) technique. The cut-off value of 0.1 that has been suggested for SVmR,[6] and which was also used for PWR in the present study, needs to be validated in a larger study.

From knowledge of the value for MAC intubation of sevoflurane in adults[19] and the relationship between MAC and MAC bar,[5] the responses after tracheal intubation found in patients not given alfentanil are unsurprising. They support the fact that haemodynamic responses to painful stimulation are not suppressed by volatile anaesthetics alone.[3]

Because the response to tracheal intubation was badly predicted by laser-Doppler SVmR, we decided to increase the stimulus applied after the first 10 patients had been studied. The stronger stimulation did not affect the predictive value of the SVmR, however, and the responses (SVmR and PWR) were similar for the two stimulation patterns. Although the two patient groups were not randomized, they did not differ except for slightly greater age in the second group. If the same concentrations of sevoflurane and nitrous oxide are given to subjects of different age, the expected effect would be greater in the older subjects.[20] In fact, the haemodynamic responses to tracheal intubation, but not the SVmR or PWR response, were significantly greater in the older subjects.

The ulnar nerve is the preferred site of stimulation to cause vasoconstriction. During neuromuscular blockade, PWR was inversely correlated with the measured alfentanil concentration regardless of the site of stimulation. Neuromuscular blockade did not suppress the PWR response a great deal and did not reduce its capacity to predict the response to tracheal intubation.

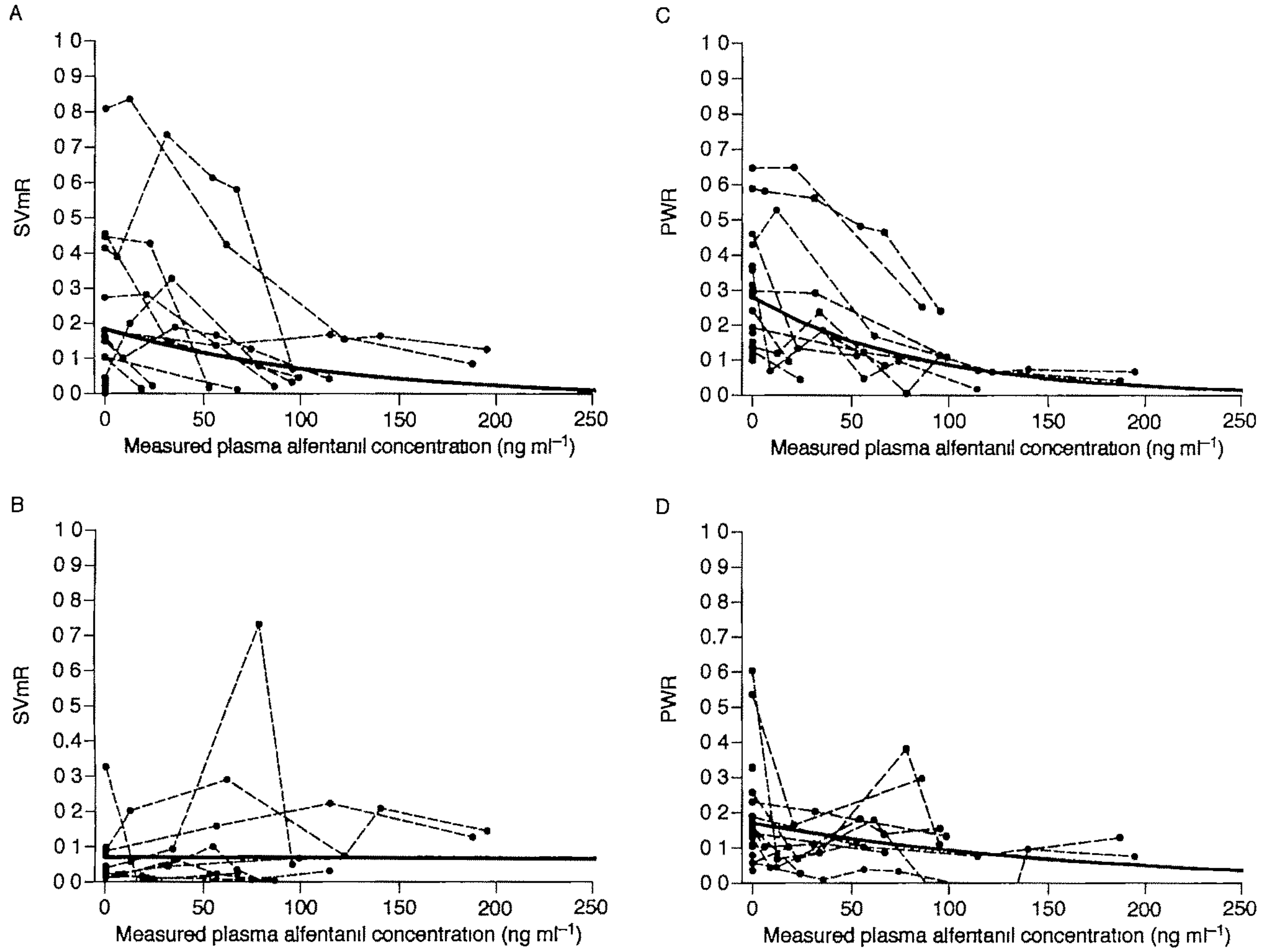


Fig 4 The laser-Doppler skin vasomotor reflex (SVmR, A and B) and pulse wave reflex (PWR, C and D) recorded after ulnar nerve (A, C) and forearm muscle (B, D) stimulation related to the corresponding measured alfentanil plasma concentrations Data points from the same subject are linked by dashed lines. The straight line indicates the best non-linear regression fit determined with NONMEM (Table 2)

Differences between our study and the previous study[6] might partly explain the lower predictive value of laser-Doppler SVmR in our study. Shimoda and co-workers[6] carried out laryngoscopy and intubation 3–5 min after i.v. induction of anaesthesia in premedicated patients, but we stimulated our patients during pharmacological steady-state conditions. We applied the first stimulus a mean (range) of 22 (21–29) min after inhalation induction and intubated 50 min (30–83) after induction. To prevent hypothermia, our patients were actively heated during the study, which increased skin temperature and induced vasodilation, shown by an increase in laser-Doppler flow and pulse wave amplitude before stimulation. Despite this vasodilation, tracheal intubation decreased pulse wave amplitude and finger blood flow (laser-Doppler). The decrease in pulse wave amplitude caused by tracheal intubation was correlated with the analgesic drug concentration, but the change in skin blood flow was not (data not shown). Because the SVmR in response to nerve stimulation was negative in nine patients, they were intubated without alfentanil administration first. The increase in arterial pressure after tracheal intubation in these patients could have increased the superficial skin blood flow in the fingers and thus reduced SVmR, because the vasodilation induced by sevoflurane and skin warming may have prevented the transient skin vasoconstriction induced by intubation. In the 11 patients given alfentanil, however, the SVmR was not suppressed and the decrease in skin blood flow was still found. Considering the whole study population, neither PWR nor SVmR was correlated with the skin temperature, so heating and sevoflurane may have suppressed skin vasomotor reactions (laser-Doppler) only in some patients. PWR was not affected by temperature, which suggests it is a better measure than SVmR.

The laser-Doppler probe measures the microvascular blood flow in a small area of the fingertip to a depth of a few millimetres. The pulse oximeter probe, in contrast, measures the changing blood volume in the whole fingertip. Finger

Table 2 PWR and SVmR and measured plasma alfentanil concentration (non-linear regression analysis). y_0=baseline reflex before the start of alfentanil administration but after neuromuscular blockade, a=non-linear regression coefficient, $\surd\sigma^2$ =SD of the reflex in an individual subject (residual and intra-individual error), −2LL=minimum value of NONMEM objective function according to the likelihood ratio test, CV=coefficient of variation in the study population computed from the interindividual error η, PWR=pulse wave reflex; SVmR=skin vasomotor reflex with site of stimulation in parentheses The inter-individual variation of the baseline reflex y_0 was considerable; the inter-individual variation of the regression coefficient a was small and did not improve the fit

Reflex	y_0	a	$\surd\sigma^2$	−2LL
PWR ulnar nerve	0.27	0.009	0.08	−167 062
SE	0.04	0.002		
CV (%)	0.60	–		
PWR muscle	0.17	0.006	0.11	−164 423
SE	0.02	0.002		
CV (%)	0.39	–		
SVmR ulnar nerve	0.19	0.008	0.13	−126 649
SE	0.05	0.003		
CV (%)	1.05	–		
SVmR muscle	0.07	3.96E–12	0.12	−163 724
SE	0.02	9.18E–06		
CV (%)	–	–		

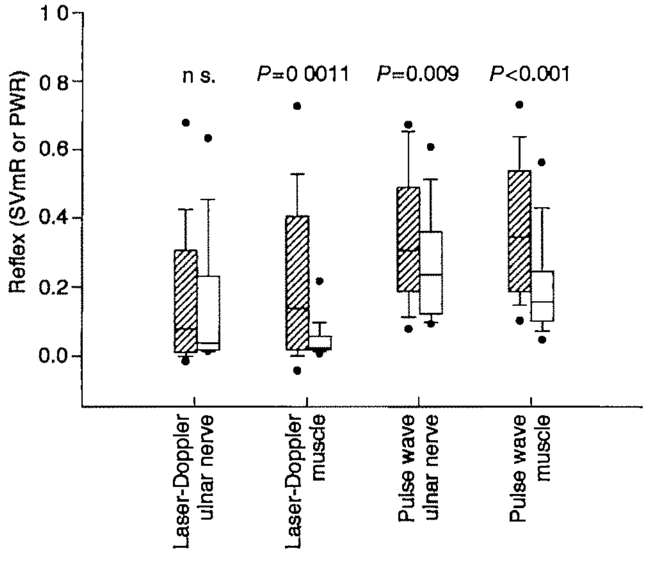


Fig 5 Laser-Doppler skin vasomotor reflex (SVmR) and pulse wave reflex (PWR) after electrical tetanic stimulation of the ulnar nerve and the flexor muscles of the forearm. Twenty stimuli before (shaded bars) and 20 stimuli after (open bars) vecuronium 0.1 mg kg^{-1} in 20 patients anaesthetized with sevoflurane (2 vol%) and nitrous oxide (50 vol% in oxygen) without opioids. Box plots with error bars representing the 10th and 90th percentiles and points the 5th and 95th percentiles

blood flow is regulated mainly by local arteriovenous shunts.[21] Vasoconstriction to a cold stimulus in awake humans is more pronounced in deep finger vessels than in superficial ones.[22] Vasoconstriction to pain in deep and superficial finger vessels has not yet been compared. Our data might suggest vasoconstriction in deep finger vessels is more pronounced than in superficial ones and is thus less suppressed by active warming of the body and volatile anaesthetics. This would explain how the PWR—in contrast to the laser-Doppler SVmR—was not attenuated in our study. Our results, in which acute sympathetic activation elicited by pain caused a transient vasoconstriction and thereby a change in the PWR, support previous data on angiotensin-induced vasoconstriction.[23] Vasoconstriction with angiotensin slightly decreased the maximal photoplethysmography wave amplitude, by reducing the size of the early systolic component of the pulse wave, while the pulse pressure and the late systolic arterial pressure in the ascending aorta increased because the reflection wave increased.[23]

We conclude that a negative SVmR does not predict a reduced response of arterial pressure or heart rate to tracheal intubation. The PWR to a 5 s, 60 mA, 50 Hz tetanic impulse to the ulnar nerve could be a better predictor and warrants further study to confirm that the selected cut-off limit is appropriate and to determine the efficiency of PWR in predicting responses in patients of different ages and medical conditions.

Acknowledgement

This research was funded by the Department of Anaesthesiology, University Hospital of Bern, Switzerland

References

1 Mangano DT, Layug EL, Wallace A, Tateo I. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter Study of Perioperative Ischemia Research Group. *N Engl J Med* 1996; **335**: 1713–20
2 Zbinden AM, Maggiorini M, Petersen-Felix S, Lauber R, Thomson DA, Minder CE. Anesthetic depth defined using multiple noxious stimuli during isoflurane/oxygen anesthesia. I. Motor reactions. *Anesthesiology* 1994; **80**: 253–60
3 Zbinden AM, Petersen-Felix S, Thomson DA. Anesthetic depth defined using multiple noxious stimuli during isoflurane/oxygen anesthesia. II. Hemodynamic reactions. *Anesthesiology* 1994; **80**: 261–7
4 Inomata S, Watanabe S, Taguchi M, Okada M. End-tidal sevoflurane concentration for tracheal intubation and minimum alveolar concentration in pediatric patients. *Anesthesiology* 1994; **80**: 93–6
5 Roizen MF, Horrigan RW, Frazer BM. Anesthetic doses blocking adrenergic (stress) and cardiovascular responses to incision—MAC BAR. *Anesthesiology* 1981; **54**: 390–8
6 Shimoda O, Ikuta Y, Sakamoto M, Terasaki H. Skin vasomotor reflex predicts circulatory responses to laryngoscopy and intubation. *Anesthesiology* 1998; **88**: 297–304
7 Shelley KH, Murray WB, Chang D. Arterial-pulse oximetry loops: a new method of monitoring vascular tone. *J Clin Monit* 1997; **13**: 223–8
8 Shelley KH, Stout B, Silverman D. The pulse oximeter waveform compared to the laser Doppler waveform. *J Clin Monit Comput* 1999; **15**: 247–8
9 Low PA, Neumann C, Dyck PJ, Fealey RD, Tuck RR. Evaluation of

skin vasomotor reflexes by using laser Doppler velocimetry. *Mayo Clin Proc* 1983; **58**· 583–92

10 Petersen-Felix S, Zbinden AM, Fischer M, Thomson DA Isoflurane minimum alveolar concentration decreases during anesthesia and surgery. *Anesthesiology* 1993; **79**: 959–65

11 Raemer DB, Buschman A, Varvel JR, *et al.* The prospective use of population pharmacokinetics in a computer-driven infusion system for alfentanil *Anesthesiology* 1990; **73**: 66–72

12 Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. *Anaesthesia* 1984; **39**: 1105–11

13 Kingsbury DP, Makowski GS, Stone JA. Quantitative analysis of fentanyl in pharmaceutical preparations by gas chromatography-mass spectrometry. *J Anal Toxicol* 1995; **19**: 27–30

14 Varvel JR, Donoho DL, Shafer SL Measuring the predictive performance of computer-controlled infusion pumps *J Pharmacokinet Biopharm* 1992; **20**: 63–94

15 Karlsson MO, Sheiner LB. The importance of modeling interoccasion variability in population pharmacokinetic analyses *J Pharmacokinet Biopharm* 1993; **21**: 735–50

16 Sheiner LB, Beal SL *NONMEM User's Guide 1994*. San Francisco (CA): University of California San Francisco, 1994

17 Rampil IJ. A primer for EEG signal processing in anesthesia. *Anesthesiology* 1998; **89**: 980–1002

18 Dutton RC, Smith WD, Rampil IJ, Chortkoff BS, Eger EI. Forty-hertz midlatency auditory evoked potential activity predicts wakeful response during desflurane and propofol anesthesia in volunteers. *Anesthesiology* 1999; **91**: 1209–20

19 Katoh T, Nakajima Y, Moriwaki G, *et al.* Sevoflurane requirements for tracheal intubation with and without fentanyl. *Br J Anaesth* 1999; **82**. 561–5

20 Mapleson WW. Effect of age on MAC in humans: a meta-analysis. *Br J Anaesth* 1996; **76**: 179–85

21 Sessler DI, McGuire J, Hynson J, Moayeri A, Heier T Thermoregulatory vasoconstriction during isoflurane anesthesia minimally decreases cutaneous heat loss *Anesthesiology* 1992; **76**: 670–5

22 Richardson D, Tyra J, McCray A Attenuation of the cutaneous vasoconstrictor response to cold in elderly men. *J Gerontol* 1992; **47**: M211–M214

23 Takazawa K, Tanaka N, Fujita M, *et al.* Assessment of vasoactive agents and vascular aging by the second derivative of photoplethysmogram waveform. *Hypertension* 1998, **32**. 365–70

British Journal of Anaesthesia 89 (3): 398–404 (2002)

Incidence and risk calculation of inotropic support in patients undergoing cardiac surgery with cardiopulmonary bypass using an automated anaesthesia record-keeping system

M. Müller[1], A. Junger[1*], M. Bräu[1], M. M. Kwapisz[1], E. Schindler[1], H. Akintürk[2], M. Benson[1] and G. Hempelmann[1]

[1]Department of Anaesthesiology and Intensive Care Medicine and [2]Department of Cardiovascular Surgery, University Hospital Giessen, Rudolf-Buchheim-Strasse 7, D-35392 Giessen, Germany

**Corresponding author*

Background. This retrospective study analysed the effects of preoperative and intraoperative factors on the occurrence of inotropic support after cardiopulmonary bypass (CPB).

Methods. The data sets of 1471 adult patients having received elective cardiac surgery with CPB were recorded using an online anaesthesia record-keeping system. Patients were judged to have required inotropic drug support if they had received one or a combination of the positive inotropic drugs, epinephrine, dobutamine and enoximone. The effects of age, height, weight, body mass index, gender, chronic heart failure, documented preoperative myocardial infarction, left main coronary artery disease, preoperative history of hypertension, chronic renal failure, diabetes mellitus, chronic obstructive pulmonary disease (COPD), preoperative medical treatment, type of surgical procedure, duration of CPB, duration of aortic clamping and reperfusion time were analysed by logistic regression for predictive power of the need for positive inotropic drugs.

Results. Of the patients, 32.4% received positive inotropic drugs in the operating theatre after weaning from CPB. The overall 30-day mortality was 2.2%. Of non-survivors, 81.8% received inotropes compared with 18.2% of survivors ($P<0.01$). The numbers of previous myocardial infarctions (odds ratio (OR), 2.01), congestive heart failures New York Heart Association class >2 (OR, 1.85), COPD (OR, 1.85) and age >65 yr (OR, 1.62), aortic cross clamping time of >90 min (OR, 2.32) and coronary artery bypass surgery (OR, 0.43) all represented influential factors within the logistic regression model.

Conclusion. The knowledge of these risk factors should be useful in increasing the anaesthetist's vigilance in those patients most at risk for inotropic support and in providing for more timely therapeutic intervention and optimizing anaesthesia management.

Br J Anaesth 2002; **89**: 398–404

Keywords: heart, cardiopulmonary bypass; heart, inotropism; records, anaesthesia, computerized; risk; surgery, cardiovascular

Accepted for publication: May 13, 2002

Depressed myocardial function is common after cardiopulmonary bypass (CPB) and cardioplegic arrest.[1] It has been described in patients with normal and decreased preoperative ejection fractions.[2] Positive inotropic drugs are frequently administered to improve post-bypass ventricular dysfunction. In some institutions, these drugs are given routinely during weaning from CPB. However, the use of positive inotropic drugs, including low dose dopamine, may be harmful in some situations (i.e. increasing myocardial oxygen consumption, dysrhythmia).

Previous investigators have focused only on intraoperative and cardiac factors,[3–5] but in this study we have investigated the hypothesis that concomitant diseases and preoperative medical treatment can influence the occurrence

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

of inotropic support after CPB. Accordingly, the main objective was to analyse the incidence and risk factors for inotropic drug support in adults undergoing cardiac surgery with CPB and to evaluate the effects of positive inotropic drugs on mortality.

Methods

From January 1, 1997 to January 5, 2000, the data sets of 1471 consecutive adult patients receiving elective cardiac surgery with cardiopulmonary bypass at the University Hospital Giessen were recorded using the online anaesthesia record-keeping system, NarkoData (IMESO GmbH, Hüttenberg, Germany).[6]

In all patients, anaesthesia consisted of weight-related doses of sufentanil, midazolam and pancuronium bromide. No patient was treated with volatile anaesthetics. CPB was performed with moderate hypothermia (rectal temperature ⩾33°C) using non-pulsatile perfusion (2.4 litres min^{-1} m^{-2}) and membrane oxygenators (Sorin 41, Sorin, Torino, Italy). Body temperature was measured using rectal (peripheral compartments) and nasopharyngeal (central compartments) probes. Priming of the extracorporeal circuit consisted of 2000 ml of Ringer's solution and 250 ml of 5% albumin solution, as well as electrolytes. Antegrade histidine tryptophane ketoglutarate (HTK) solution was introduced for cardioplegic arrest. The acid–base management followed the alpha-stat procedure, and the haematocrit was held between 20 and 30% throughout CPB.

The reperfusion period before weaning from CPB was one third of the aortic cross-clamping time. After achieving a rectal temperature ⩾35°C, weaning from CPB was performed by a gradual filling of the heart to a systolic blood pressure of 90–100 mm Hg or a maximum diastolic pulmonary artery pressure of 20 mm Hg and successively reducing pump flow without routine use of inotropes. Patients received inotropes either based on the observation of reduced cardiac contractility during and after weaning (by direct visual inspection of the right ventricle and/or transoesophageal echocardiography) or after measuring a reduced cardiac index (<2.0 litres min^{-1} m^{-2} measured by thermodilution), or both.

Structure query language statements were defined in order to retrospectively extract data from the database. Patients were judged to have required inotropic drug support if they had received one or a combination of the inotropes, epinephrine, dobutamine or enoximone, as a single dose or infusion. The cardiac anaesthesia risk evaluation (CARE) score[7] was used for risk calculation and the 30-day mortality was evaluated.

A total of 20 patient-related variables and four operative ones were investigated for predictive power. The patient-related variables were age, height, weight, body mass index (BMI), gender, chronic heart failure (New York Heart Association (NYHA) function class at presentation), documented preoperative myocardial infarction, left main coronary artery disease, preoperative history of hypertension, chronic renal failure (permanent increase in serum creatinine >1.1 mg dl^{-1}), preoperative ejection fraction (assessed by ventriculography), diabetes mellitus (non-insulin-dependent and insulin-dependent), chronic obstructive pulmonary disease (COPD) (documented asthma, chronic bronchitis or pulmonary emphysema), and preoperative treatment with angiotensin converting enzyme inhibitors (ACEI), diuretics, digoxin, β-adrenergic blockers, calcium-antagonists, nitroglycerin or antidysrhythmic drugs. Data for the preoperative ejection fraction were only available in 428 patients and were therefore not included in the logistic regression. The surgical variables included the type of surgical procedure (coronary artery bypass (CABG) surgery, cardiac valve surgery or both simultaneously), duration of CPB, duration of aortic cross-clamping and reperfusion time.

Data were exported from the database into the SPSS® statistics program (SPSS Software GmbH, München, Germany) in order to perform statistical analysis. The dichotomous variable, positive inotropic drugs (yes/no), was used as the target criterion. Univariate analysis was performed using the *t*-test for metrically scaled variables. Categorical variables were assessed for a significant association with inotropic support using either the χ^2 test or the exact Fisher test. Data sets were randomly divided into an evaluation (n=761) and validation (n=710) set. The evaluation data set was examined by stepwise logistic regression analysis. Logistic regression was used to filter predictor variables having a significant influence on positive inotropic drugs within a multivariate model. Furthermore, logistic regression was used to estimate the coefficients (β) of these variables. Based on the results, the probability (score) of the event 'positive inotropic drugs: yes' may be estimated using a logistics function. A forward stepwise algorithm (inclusion criteria: log likelihood test ratio based on maximum likelihood function) was used for developing a logistic regression model. At each step, independent variables not yet included in the equation were tested for possible inclusion. The variable with the strongest significant contribution (P<0.05) improving the model was included. Variables already included in the logistic regression equation were tested for exclusion based on the probability of a log likelihood test ratio. The analysis ended when no further variables for inclusion or exclusion were available. Variables in the logistic regression equation were defined as 1 if present and 0 if absent. Constant values were calculated as absolute values.

We used the Hosmer–Lemeshow goodness-of-fit H statistic to evaluate the overall calibration of the model equation in the validation set. This was accomplished by testing the null hypothesis that the mean predicted and observed incidence of inotropic support was equal.[8] [9] For this reason, the hypothesis has to be retained for confirming the fitness of the model. The level of significance should be at least P>0.05, but preferably P>0.2 to allow an indirect control of the β-failure. The observed and expected incidences of inotropic support are shown graphically in calibration curves with the number of patients per group.

The discriminative power of the model was assessed with a receiver operating characteristic (ROC) curve.[10] The ROC curve plots the percentage of true positive values (sensitivity) based on the individual score against the percentage of false positive values (1–specificity). The area under the curve indicates the accuracy of the calculated model between 0 and 1. This may be interpreted as the probability of correct patient classification in one of the two categories (positive inotropic drugs: yes or no). An area of 0.5 indicates that the predictive accuracy equates a random selection.

Results

Altogether, inotropic drug support after weaning from CPB was used in 476 of the 1471 patients (32.4%). Epinephrine was used as a sole inotrope in 283 patients, dobutamine in 39 patients and enoximone in 29 patients. Epinephrine and enoximone were used in 106 patients as a two-drug positive inotropic drug combination, and epinephrine and dobutamine were used together in 15 patients. Epinephrine, dobutamine and enoximone were given in combination to four patients. Of the 1471 patients, 1140 underwent CABG surgery, 231 had cardiac valve surgery and 100 underwent simultaneous surgery of the cardiac valves and CABG.

The mean CARE score was comparable between patients with positive inotropic drugs (2.6 (SD 0.7)) and patients without positive inotropic drugs (2.6 (0.6)). The overall 30-day mortality was 2.2%. However, 27 of 33 non-survivors (81.8%) received positive inotropic drugs (P<0.01 compared with survivors) and 449 of 1438 survivors received positive intropic drugs.

The results of the univariate analysis concerning the influence of studied variables on the occurrence of positive inotropic drugs are presented in Tables 1 and 2. Mean values of metrically scaled variables are shown in Table 1. Table 2 shows the distribution of ordinally and nominally scaled variables and their relations to the incidence of receiving positive inotropic drugs

The following factors had a significant influence on the use of positive inotropic drugs: age, gender, weight, congestive heart failure, myocardial infarction, ejection fractions, renal failure, COPD, preoperative use of diuretics, digitalis and β-adrenergic blockers, type of surgery, duration of surgery, CPB time, aortic cross-clamping time and reperfusion time. In contrast to these, height, BMI, left main coronary artery disease, history of hypertension, diabetes mellitus, long-term therapy with ACE inhibitors, calcium-blocking drugs, nitroglycerin and antidysrhythmic drugs did not influence the use of positive inotropic drugs.

The results of stepwise logistic regression analysis are summarized in Table 3. Among patient-related factors, the number of previous myocardial infarctions showed the strongest association (OR, 2.01), indicating a twofold increased risk per myocardial infarction for the use of positive inotropic drugs. Having a congestive heart failure NYHA class of >2 (OR, 1.85), COPD (OR, 1.85) and age >65 yr (OR, 1.62) also represented patient-related influential factors. Regarding the surgical variables within the logistic regression model, the risk increased most with an aortic cross-clamping time of >90 min (OR, 2.32), whereas CABG surgery possessed a positive influence (OR, 0.43).

Table 1 Mean values (SD or range) of metrically scaled predictors of positive inotropic drugs in the univariate analysis *P<0.01 (t-test)

Variables	**No positive inotropic drugs (n=995)**	**Positive inotropic drugs (n=476)**
Age (yr)*	63.9 (58–71)	66.5 (61–73)
Height (cm)	170.9 (9.1)	169.7 (8.8)
Weight (kg) *	79.7 (12.6)	76.5 (12.4)
BMI (kg m^{-2})	27.4 (6.3)	26.5 (3.7)
Duration of surgery (min)*	210.2 (53.8)	222.0 (66.0)
CPB time (min)*	103.9 (30.4)	116.8 (40.0)
Aortic cross-clamping time (min)*	64.2 (20.1)	70.2 (26.2)
Reperfusion time (min)*	34.4 (13.5)	40.4 (17.6)

The probability for the need of positive inotropic drugs (P_{PID}) during and after weaning from CPB could be calculated by the following logistic equation, Equation 1.

$$P_{\mathrm{PID}}=1/(1+e^{-z}) \qquad (1)$$

where $z=-0.8524 \times (\mathrm{CABG})+0.6141 \times$ (congestive heart failure NYHA >2) + $0.6976 \times$ (number of myocardial infarctions) + $0.6156 \times$ (COPD) + $0.4823 \times$ (age >65 yr) + $0.8421 \times$ (aortic cross-clamping time >90 min) − 1.1886.

The factors for CABG, congestive heart failure NYHA >2, COPD, age >65 yr and aortic cross-clamping time >90 min were defined as 1 if present and 0 if absent. By notating number of myocardial infarctions, the number of previous myocardial infarctions is used as the factor.

ORs were determined by a logistical function for the validation set. The resulting probabilities were used for calculating the ROC curve (Fig. 1). The area under the ROC curve, acting as the measure of accuracy, was 0.68. The 95% confidence interval is represented by area (0.64–0.72). The results of the Hosmer–Lemeshow H statistic showed acceptable calibration (H=12.7; P=0.09; degrees of freedom, 7). The calibration curve (Fig. 2) plots the observed and expected positive inotropic drug frequency together with the number of categorized patients (bar diagram), depending on the probability of inotropic support

A sensitivity of 0.53 and a specificity of 0.73 were obtained using a probability of 0.38, a value having the best relationship between sensitivity and specificity as a threshold for factor inclusion. The score of correctly categorized patients based on this threshold is 0.67. Other values and their respective variables can be used, including sensitivity, specificity and the total number of correctly categorized patients based on other limits. These can be ascertained using the ROC curve (Fig. 1).

Table 2 Results of the univariate analysis concerning the influence of studied variables on the occurrence of positive inotropic drugs. Exactitude test according to Fisher or χ^2 test for independence. $^*P<0.01$ between the groups

	Total	**No positive inotropic drugs**		**Positive inotropic drugs**	
	n	*n*	%	*n*	%
Gender*					
Female	380	232	23.4	148	31.1
Male	1089	761	76.6	328	74.1
Type of surgery*					
CABG	1140	831	83.5	309	64.9
Valvular surgery	231	118	11.9	113	23.7
Valvular and CABG	100	46	4.6	54	11.3
Congestive heart failure*					
No	1023	731	73.5	292	61.3
NYHA class 1	25	22	2.2	3	0.6
NYHA class 2	214	141	14.2	73	15.3
NYHA class 3	198	100	10.1	98	20.6
NYHA class 4	11	1	0.1	10	2.1
Myocardial infarction*					
0	913	631	63.5	282	59.6
1	472	331	33.3	141	29.8
2	71	27	2.7	44	9.3
3	10	4	0.4	6	1.3
Left main coronary artery disease					
No	1268	852	85.8	416	87.9
Yes	198	141	14.2	57	12.1
Preoperative ejection fraction*					
>50%	302	220	80.6	82	52.9
30–50%	100	50	18.3	50	32.3
<30%	26	3	1.1	23	14.8
Preoperative history of hypertension					
No	421	269	27.1	152	32.1
Yes	1045	724	72.9	321	67.9
Renal failure*					
No	1251	872	87.8	379	80.1
Yes	215	121	12.1	94	19.9
Diabetes mellitus					
No	1115	766	77.1	349	73.8
Yes	351	227	22.9	124	26.2
COPD*					
No	1235	854	85.8	381	80
Yes	236	141	14.2	95	20
ACEI					
No	914	624	62.8	290	61.3
Yes	552	369	37.2	183	38.7
Diuretics*					
No	1121	806	81.2	315	66.6
Yes	345	187	18.8	158	33.4
Digitalis*					
No	1343	939	94.6	404	85.4
Yes	123	54	5.4	69	14.6
β-adrenergic blockers*					
No	823	532	53.6	291	61.5
Yes	643	461	46.4	182	38.5
Calcium blockers					
No	1161	780	78.5	381	80.5
Yes	305	213	21.5	92	19.5
Nitroglycerin					
No	751	494	49.7	257	54.3
Yes	715	499	50.3	216	45.7
Antidysrhythmic drugs					
No	1347	909	91.5	438	92.6
Yes	119	84	8.5	35	7.4
Aortic cross-clamping time*					
<90 min	1304	909	69.7	395	30.3
>90 min	137	86	51.5	81	48.5

Table 3 Results of logistic regression analysis in the multivariate analysis

Variables	**β**	**SE**	***P*-value**	**OR**	**95% confidence interval of OR**
Type of surgery: CABG	−0.8524	0.33345	<0.01	0.4264	0.2213–0.8214
Congestive heart failure, NYHA >2	0.6141	0.2342	<0.01	1.8481	1.1679–2.9244
Number of myocardial infarctions	0.6976	0.1487	<0.01	2.0090	1.5011–2.6888
COPD	0.6156	0.2245	<0.01	1.8508	1.1919–2.8739
Age >65 yr	0.4823	0.1763	<0.01	1.6197	1.1464–2.2885
Aortic cross-clamping time, >90 min	0.8421	0.2823	<0.01	2.3212	1.3348–4.0363
Constant	−1.1886	0.3550	<0.01		

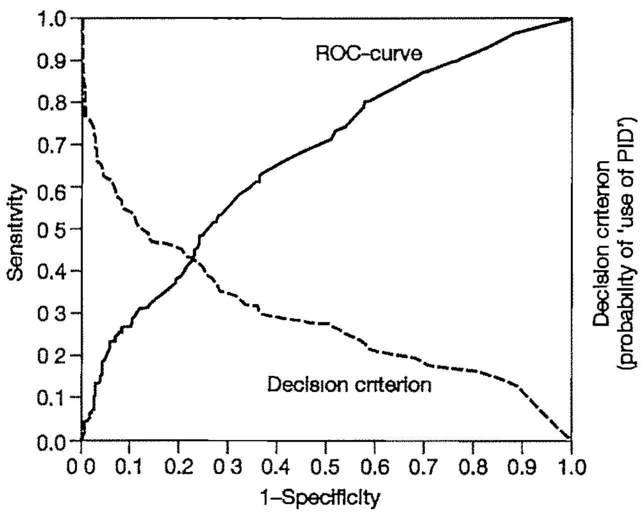


Fig 1 Receiver operating characteristics (ROC) curve including risk score (decision criterion). The area under the ROC curve is 0.68 with a 95% confidence interval from 0.67 to 0.72. PID, positive inotropic drugs.

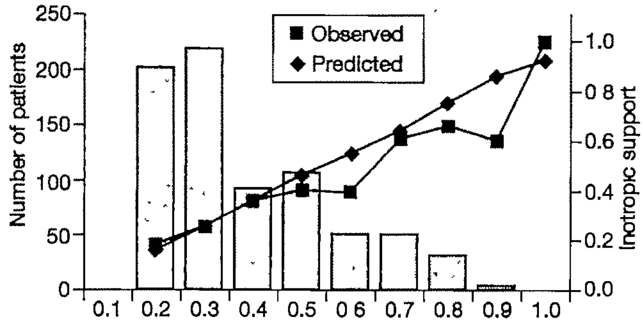


Fig 2 Comparison of predicted and observed frequencies of positive inotropic support depending on the probability of occurrence (validation set). The corresponding number of patients is displayed in a bar diagram.

Discussion

In the present study, 32% of the patients had a post-CPB ventricular dysfunction requiring inotropic drug support. Patients receiving positive inotropic drugs had a higher 30-day mortality compared with those without positive inotropic drugs. This suggests that the use of inotropes following CPB is not only a variable process in the present setting but indicates a poor early outcome. It has recently been shown that late survival is significantly reduced in patients with non-fatal perioperative cardiac outcomes such as perioperative myocardial infarction or low cardiac output syndrome.[11]

Butterworth and colleagues[3] reported that positive inotropic drugs were given in 52% of patients undergoing cardiac valve surgery, a frequency comparable to patients undergoing CABG surgery in a study from Royster and colleagues.[4] Rao and colleagues[5] reported an overall prevalence of low cardiac output after CABG surgery, defined as the need for a postoperative intra-aortic balloon pump or inotropic support in the intensive care unit of 9.1%. However, in contrast to Rao and colleagues, we studied a case mix (CABG surgery and/or cardiac valve surgery) in which CABG surgery correlates with a lower incidence of positive inotropic drugs. Furthermore, Rao and colleagues defined in their study that patients receiving a 'renal' dose of dopamine do not suffer from low cardiac output. A recent study has shown that dosing dopamine based on body weight does not yield consistent, predictable plasma concentrations.[12] Thus, stimulating effects of a 'renal' dose on cardiac β-receptors cannot be excluded. Inotropes, including dopamine at doses <5 μg kg^{-1} min^{-1}, were not routinely administered during and after weaning from CPB at our institution. The use of positive inotropic drugs thus represented failure of our usual therapeutic regimen and indicated a poor ventricular function, at least in the first hours after CPB.

In the present study, CABG surgery was associated with a lower incidence of positive inotropic drugs than were cardiac valve surgery and combined valve and CABG surgery. The strongest independent association with positive inotropic drugs was found among factors of impaired preoperative ventricular function (number of pre-existing myocardial infarctions and anamnestic congestive heart failure NYHA class >2). A close association between congestive heart failure NYHA class >2 and mortality and morbidity after cardiac surgery has been described.[7] A low preoperative ejection fraction has also been identified by other investigators as a predictor of low cardiac output after CPB in patients undergoing CABG surgery as well as in those undergoing valve surgery.[3 4] In a subgroup of 428 patients, we analysed the influence of the ejection fraction. A significant influence of a depressed ejection fraction on positive inotropic drug frequency could be observed in this subgroup as well. However, the ejection fraction was not included in the multivariate analysis because it was less well documented compared with the NYHA classification of congestive heart failure.

Our results demonstrate that patients with COPD have an increased risk of needing positive inotropic drugs. Patients with COPD commonly have a mild-to-moderate increase in pulmonary artery pressure.[13] An increased afterload may influence right ventricular performance after CPB. Weightman and colleagues[14] have shown that chronic lung disease increases the risk of in-hospital mortality after CABG surgery.

An age of >65 yr indicates an increased risk for inotropic support in the present study. Advanced age is always accompanied by a general decline in organ function, especially because of changes in the structure and function of the heart and vasculature that will ultimately affect cardiovascular performance, even in the absence of overt coexisting diseases.[15] This may explain why post-ischaemic systolic functional recovery was markedly worse in the older group of an ovine model.[16]

With regards to intraoperative factors, we found that an aortic cross-clamping time of >90 min is an independent predictor of post-CPB need for positive inotropic drugs. A greater need for inotropic agents during long periods of aortic cross-clamping time was also observed by Bar-El and colleagues.[17] To achieve cardioplegic arrest, cold (4°C) crystalloid cardioplegia, HTK solution, was applied by hydrostatic pressure as a single shot into the aortic root or directly into the coronary ostia when necessary. On rare occasions, a further dose was given via a venous graft during CABG surgery. Using this strategy for cardioplegic arrest, a prolonged cross-clamping time can result in a decrease in adenosine triphosphate compared with blood cardioplegia.[18] In a study comparing blood and crystalloid cardioplegia in patients with unstable angina, blood cardioplegia significantly reduced the incidence of perioperative myocardial infarction, low-output syndrome and operative mortality.[19]

One major limitation is that we have not been able to assess the impact of the quality of surgery (i.e. perioperative myocardial infarction, re-operation). The CARE score was used for risk adjustment. The overall mean CARE score was 2.6. A CARE score of 3.0 predicts a mortality rate of 2.2%,[7] which is comparable to our overall 30-day mortality. However, we could not predict the need of inotropic support by using the CARE score.

To conclude, we have shown that preoperative myocardial infarction, congestive heart failure NYHA class >2, COPD, age >65 yr and aortic cross-clamping time >90 min are independent predictors of ventricular dysfunction after CPB requiring inotropic support. Using the described anaesthetic strategy, inotropes following CPB are associated with higher 30-day mortality. However, the knowledge of these risk factors should be useful in increasing the anaesthetist's vigilance in those patients most at risk for inotropic support and in providing for more timely therapeutic intervention and optimizing anaesthesia management.

Acknowledgement

We thank Moredata GmbH, Giessen, for their help in data management and statistical evaluation.

References

1 Breisblatt WM, Stein KL, Wolfe CJ, et al. Acute myocardial dysfunction and recovery: a common occurrence after coronary bypass surgery. *J Am Coll Cardiol* 1990; **15**: 1261–9

2 Mangano DT. Alteration of ventricular function during coronary artery surgery *Acta Chir Scand Suppl* 1989; **550**. 57–62

3 Butterworth JF, Legault C, Royster RL, Hammon JW Jr. Factors that predict the use of positive inotropic drug support after cardiac valve surgery. *Anesth Analg* 1998; **86**: 461–7

4 Royster RL, Butterworth JF, Prough DS, et al. Preoperative and intraoperative predictors of inotropic support and long-term outcome in patients having coronary artery bypass grafting. *Anesth Analg* 1991; **72**: 729–36

5 Rao V, Ivanov J, Weisel RD, Ikonomidis JS, Christakis GT, David TE. Predictors of low cardiac output syndrome after coronary artery bypass. *J Thorac Cardiovasc Surg* 1996; **112**. 38–51

6 Benson M, Junger A, Quinzio L, et al. Clinical and practical requirements of online software for anesthesia documentation an experience report. *Int J Med Inf* 2000; **57**: 155–64

7 Dupuis JY, Wang F, Nathan H, Lam M, Grimes S, Bourke M. The cardiac anesthesia risk evaluation score· a clinically useful predictor of mortality and morbidity after cardiac surgery. *Anesthesiology* 2001; **94**: 194–204

8 Hosmer DW, Lemeshow S. *Applied Logistic Regression*. New York· John Wiley and Sons Inc., 1989

9 Hosmer DW, Hosmer T, Le Cessie S, Lemeshow S. A comparison of goodness-of-fit tests for the logistic regression model. *Stat Med* 1997; **16**: 965–80

10 Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982, **143**: 29–36

11 Fremes SE, Tamariz MG, Abramov D, et al. Late results of the Warm Heart Trial: the influence of nonfatal cardiac events on late survival. *Circulation* 2000; **102**: III339–45

12 MacGregor DA, Smith TE, Prielipp RC, Butterworth JF, James RL, Scuderi PE. Pharmacokinetics of dopamine in healthy male subjects. *Anesthesiology* 2000; **92**: 338–46

13 Weitzenblum E. The pulmonary circulation and the heart in chronic lung disease. *Monaldi Arch Chest Dis* 1994, **49**: 231–4

14 Weightman WM, Gibbs NM, Sheminant MR, Whitford EG, Mahon BD, Newman MA. Drug therapy before coronary artery surgery: nitrates are independent predictors of mortality and beta-adrenergic blockers predict survival. *Anesth Analg* 1999; **88**: 286–91

15 Priebe HJ. The aged cardiovascular risk patient. *Br J Anaesth* 2000; **85**: 763–78

16 Misare BD, Krukenkamp IB, Levitsky S. Age-dependent

British Journal of Anaesthesia **89** (3) 405–8 (2002)

Delays in defibrillation: influence of different monitoring techniques

G. D. Perkins[1]*, C. Roberts[2] and F. Gao[1]

[1]Department of Intensive Care Medicine and [2]Resuscitation Training Department, Birmingham Heartlands Hospital, Bordesley Green East, Birmingham B9 5SS, UK

**Corresponding author*

Background. Rapid defibrillation is the most important intervention required for a patient in cardiac arrest due to ventricular fibrillation or ventricular tachycardia. Isolated case reports of spurious asystole may have seen a change in practice, moving away from monitoring through defibrillator paddles and gel pads in favour of attaching electrocardiograph (ECG) leads for the initial monitoring of a collapsed patient. We surveyed current preferences for initial monitoring and estimated the difference in time taken to deliver the first shock with the following three monitoring techniques: defibrillator paddles and gel pads, ECG leads and hands-free adhesive pads.

Methods. Sixty Advanced Life Support (ALS) course directors, selected at random, were questioned to establish their current practice. Twenty ALS providers received 5 min revision in the three techniques for the initial monitoring of a collapsed patient and were then randomly tested to measure the time from confirmation of arrest to the first shock.

Results. Forty-two directors indicated their preferred methods for initial monitoring as 74% leads, 21% paddles and 5% hands-free adhesive pads. Before testing, 10 providers preferred paddles and 10 preferred leads. Monitoring through leads 54 (range 49–65) s was significantly slower than paddles 28 (24–31) s, *P*<0.01 and adhesive pads 23 (19–27) s, *P*<0.01. There was no significant difference in the time taken between paddles and adhesive pads.

Conclusion. The current practice of monitoring through leads delays the time to deliver the first shock. We recommend that initial monitoring through leads be discontinued in favour of hands-free adhesive pads or defibrillator paddles/gel pads.

Br J Anaesth 2002; **89**: 405–8

Keywords: complications, cardiac arrest; equipment, defibrillators; monitoring, electrocardiography

Accepted for publication: April 20, 2002

Since the first descriptions over 50 years ago, defibrillation has become established as the standard treatment of a patient in cardiac arrest due to ventricular fibrillation (VF) or ventricular tachycardia (VT).[1] The critical importance of early defibrillation has been clearly shown in several large, prospective clinical studies. Delays in defibrillation are associated with poor outcome.[2–5] Outside the monitored environment of the operating theatre, coronary and intensive care units, the underlying rhythm in the collapsed patient needs to be determined rapidly. Three techniques are currently available: defibrillator paddles and gel pads, standard ECG leads, or hands-free adhesive gel pads.

In 1999 the medical devices agency issued a safety notice warning that spurious asystole might be diagnosed in error after attempted defibrillation using paddles and gel pads.[6] A further report was published shortly afterwards in the *British Medical Journal* of a similar episode at a district general hospital in England,[7] when a patient was monitored using gel pads with defibrillator paddles. After delivering a shock, a period of apparent asystole was noted on the defibrillator monitor (shown as a continuous or broken line); however, simultaneous electrocardiographic (ECG) lead monitoring with independent electrodes showed that the patient remained in VF. Without additional monitoring with ECG leads, a delay in the delivery of further shocks would have resulted. Despite the limited number of reports of spurious asystole in the literature,[6–8] the wide publicity these reports have received may have changed practice from the rapid

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Table 1 ALS course directors' initial monitoring preferences

	n (%)
ECG leads	31 (74)
Defibrillator paddles and gel pads	9 (21)
Hands-free adhesive pads	2 (5)

paddles/gel pad technique to monitoring initially through standard ECG leads.

We set out to determine current preferences for the initial monitoring of the collapsed patient and to measure the difference in time taken to deliver the first shock with the following three monitoring techniques: defibrillator paddles and gel pads, ECG leads, and hands-free adhesive pads.

Methods

The study was divided into two parts. In the first part, 60 electronic questionnaires were sent to Advanced Life Support (ALS) course directors selected randomly from the Resuscitation Council UK register of course directors in September 2001. Course directors are experienced ALS trainers with medical, nursing or paramedical backgrounds who have been granted permission to lead the Resuscitation Council UK Advanced Life Support Provider Course. A follow-up telephone call to non-responders was made 2 months later. The questionnaire asked the course directors to specify their preference and teaching practice for the initial monitoring of the collapsed patient.

In the second part of the study, 20 doctors or nurses were recruited without prior warning to perform a defibrillation test. All subjects had undertaken the Resuscitation Council UK Advanced Life Support Provider Course and were working at Birmingham Heartlands Hospital. The subject's preference for initial monitoring was recorded before testing. Five minutes of revision time was given in a standardized manner, covering the three different techniques for initial monitoring that were to be tested. These three techniques were: (i) defibrillator paddles and gel pads, where gel pads (defib-pads; 3M, Germany) and defibrillator paddles are placed on the patient's chest; (ii) ECG leads, where three standard ECG (3M-red-dot; 3M, Germany) electrodes are used for monitoring and gel pads/paddles are used for defibrillation; and (iii) hands-free adhesive pads (Multi-function Adult electrode pads; Hewlett Packard, UK), which are adhesive electrode pads used for monitoring and defibrillation. All tests were undertaken on a Laerdal adult ALS manikin skill trainer using a Heartsim 200 rhythm simulator (Laerdal Medical, Norway). The Codemaster XL (Hewlett Packard) defibrillator was used for all tests, with default monitoring set to 'paddles' for monitoring through paddles/gel pads, and 'leads' (lead II) for ECG leads and hands-free adhesive pad tests. There was no significant difference in charge time between the defibrillators used (2.4 (range 2.4–2.4) s for defibrillator 1 compared to 2.3 (2.3–2.4) s for defibrillator 2 during 10 successive shocks $P>0.05$). The training manikin is designed to have the ECG leads attached directly onto the chest wall and therefore it was not possible to obtain reliable ECG signals by attaching the ECG electrode dots to the ECG monitoring points. To reflect clinical practice, subjects actually attached leads and electrodes to the manikin's chest, but the ECG signal was fed directly to the defibrillator after the third lead had been attached correctly.

The subjects were then presented with three simulated defibrillation tests in a randomized order (block randomization). The manikin was stated to be in cardiac arrest and the subject was required to establish initial monitoring, determine the underlying rhythm and deliver the first shock. The time taken from the start of each test until the defibrillator was charged to 200 J (as indicated by the defibrillator audible warning bleep) was recorded.

Statistical analysis

Data were entered into Excel 97 (Microsoft, NY, USA) and analysed using SPSS 10.0 for windows (SPSS Inc., Chicago, IL, USA). Monitoring preferences from all subjects were analysed using χ^2 and Fisher's exact tests. Defibrillation test data were analysed for normality and found to be in a non-normal distribution. Friedman's repeated measures analysis of variance (ANOVA) on ranks with Dunnett's test was used for multiple comparisons between the three monitoring techniques. Data were expressed as medians (interquartile range). A P value <0.05 was considered statistically significant.

Results

In part 1 of the study, 42 (70%) course directors replied to the questionnaire. The majority (74%) indicated that their preferred method of initial monitoring of the collapsed patient was ECG leads (Table 1). In part 2 of the study, 10 nurses and 10 doctors were recruited for the defibrillation test. The median duration from attendance on the Advanced Life Support Provider Course was 7.5 months (range 1–48 months). Ten subjects reported defibrillator paddles and gel pads and 10 reported ECG leads as their preferred initial monitoring technique. There was no statistical difference in preferences between subjects trained >24 months previously (i.e. before the first reports of spurious asystole) and those trained more recently (P=0.63).

The time taken to deliver the first shock using ECG leads was 54 (49–65) s compared with defibrillator paddles and gel pads 28 (24–31) s; $P<0.01$ and hands-free adhesive pads 23 (19–27) s; $P<0.01$. There was no significant difference in the time taken between paddles and hands-free adhesive pads (Fig. 1).

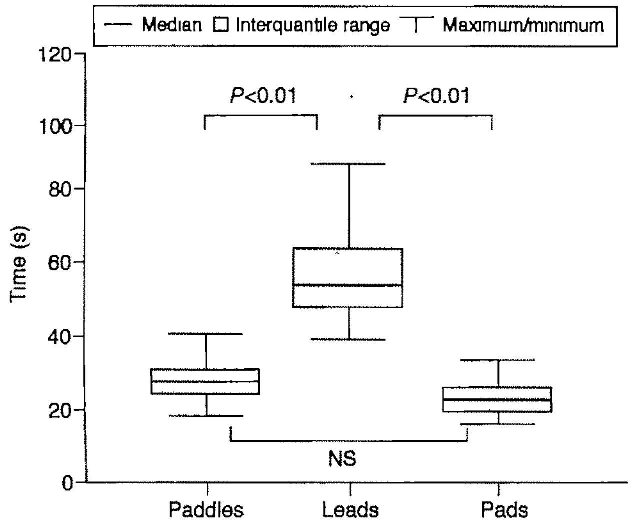


Fig 1 Box plot of time taken to deliver first shock

Discussion

The principal findings of this study are that contrary to current guidelines,[9] most ALS course directors recommend that initial monitoring is performed using ECG leads. We found that this delays the delivery of the first shock on average by 26.4 s compared with defibrillator paddles and gel pads, and by 31 s compared with hands-free adhesive pads.

A potential limitation of our findings from the questionnaire survey to ALS course directors is the moderate response rate. However, the clear preference (74%) for monitoring initially through ECG leads amongst the respondents suggests that this teaching practice is widespread. The second part of this study consisted of a simulated cardiac arrest using a resuscitation manikin and has several inherent limitations. First, the prior revision and controlled environment of the laboratory test is likely to have shortened the time to first shock for all tests, as the equipment was immediately available and defibrillator operators were probably more relaxed than during a genuine cardiac arrest. Secondly, the signal quality obtained through the resuscitation manikin may be different from that seen in clinical practice, although our experience is that it is similar irrespective of which monitoring technique is used. The poor quality signals seen when attaching ECG leads and electrodes to the manikin may have artificially increased the time taken to deliver the first shock with this technique. However, this was identified in a pilot study and overcome by feeding the electrical signal directly from the rhythm simulator to the defibrillator during the actual study. Despite these limitations, the findings of this study can probably reasonably be extrapolated to the clinical environment.

After the early reports of spurious asystole, Bradbury and colleagues conducted an *in vitro* study to investigate this phenomenon.[10] Using a low (50 Ω) and high impedance (1050 Ω) defibrillator test model they measured the time delay in the return of a test signal following defibrillation through gel pads and hands-free adhesive pads. They found significant delays (up to 61 s) in the return of the test signal with the gel pad/paddle combination using the high impedance test model after several shocks. This was caused by retention of the electrical charge by the gel pads. However, no such delays in the return of the test signal occurred with the low impedance system or when hands-free adhesive pads were used with either system. As the low impedance test model is closer to the reported mean transthoracic impedance of patients in cardiac arrest,[11] they concluded that the results supported their clinical observations that spurious asystole is relatively rare in practice. In addition spurious asystole occurs only after several successive shocks so this should not influence the choice of initial monitoring. If after two or three shocks the rare phenomenon of spurious asystole is seen on the monitor, then ECG lead monitoring should be rapidly established.

Whilst our experience and that of others[7 10] suggests that spurious asystole occurs only rarely, no prospective studies have formally investigated this phenomenon. A recent study examining the recurrence of VF following defibrillation with automated external defibrillators (and hands-free adhesive pads) in the pre-hospital environment reported delays in the recurrence of VF of >30 s in half of all the patients studied.[12] To our knowledge there have been no reported cases of spurious asystole occurring with the hands-free adhesive pads. The work by Bradbury and colleagues[10] suggests that it is unlikely to occur with this device. However, only simultaneous ECG lead monitoring can determine if some of these delays could be attributable to spurious asystole, and further prospective studies are required.

The choice of initial monitoring technique in cardiac arrest is considered an important issue in resuscitation training. We have recently reported that in a group of 25 ALS instructors, five considered that initial monitoring with defibrillator paddles and gel pads without simultaneous ECG lead monitoring constituted unacceptable performance,[13] although current guidelines recommend the defibrillator paddles and gel pads technique for initial monitoring.[9] At present we are aware of only a handful of high profile case reports reporting the phenomena of spurious asystole.[6–8 14] Monitoring though ECG leads may delay defibrillation by on average 30 s. Early defibrillation improves survival from cardiac arrest,[2–4 11 16] and extrapolating the data presented in the modified Larsen model for survival from cardiac arrest[5 17] it can be anticipated that delays in defibrillation of this order may reduce survival by 3.5–5%.

In the absence of convincing data that spurious asystole is common, we recommend that in the unmonitored collapsed patient, initial monitoring through leads should not be used, and hands-free adhesive pads or defibrillator paddles and gel pads should be; however, if asystole or apparent loss of signal occurs after defibrillation with defibrillator paddles and gel pads then monitoring with ECG leads should be established as soon as possible. After the first three shocks are given, the ECG leads can then be attached if appropriate while basic life support is initiated. This recommendation is consistent with the advice recently published in the Resuscitation Council UK Instructor Bulletin.

References

1 de Latorre F, Nolan J, Robertson C, Chamberlain D, Baskett P. European Resuscitation Council Guidelines 2000 for Adult Advanced Life Support. A statement from the Advanced Life Support Working Group (1) and approved by the Executive Committee of the European Resuscitation Council. *Resuscitation* 2001; **48**: 211–21

2 Eisenberg MS, Hallstrom AP, Copass MK, *et al*. Treatment of ventricular fibrillation. Emergency medical technician defibrillation and paramedic services. *JAMA* 1984; **251**: 1723–6

3 Weaver WD, Copass MK, Bufi D, *et al*. Improved neurologic recovery and survival after early defibrillation. *Circulation* 1984; **69**: 943–8

4 Valenzuela TD, Roe DJ, Cretin S, Spaite DW, Larsen MP. Estimating effectiveness of cardiac arrest interventions: a logistic regression survival model. *Circulation* 1997; **96**: 3308–13

5 Larsen MP, Eisenberg MS, Cummins RO, Hallstrom AP. Predicting survival from out-of-hospital cardiac arrest: a graphic model. *Ann Emerg Med* 1993; **22**: 1652–8

6 Medical Devices Agency (MDA). Hewlett Packard Codemaster XL, XL+, 100 defibrillators. Problem. Possible loss of ECG monitoring via paddles following defibrillation using gel pads. SN 9819. London: MDA, 1998

7 Chamberlain D. Spurious asystole with use of manual defibrillators. Users should not rely on monitoring through paddles, using any type of gel pad, once shocks have been delivered. *Br Med J* 1999; **319**: 1574–5

8 MDA Conductive gel pads for defibrillation for cardioversion. SN1999(40). London: MDA, 2000

9 Resuscitation Council UK. *Advanced Life Support Course Provider Manual*. 4th Edn. London: Resuscitation Council, 2000

10 Bradbury N, Hyde D, Nolan J. Reliability of ECG monitoring with a gel pad/paddle combination after defibrillation. *Resuscitation* 2000; **44**: 203–6

11 Poole JE, White RD, Kanz KG, *et al*. Low-energy impedance-compensating biphasic waveforms terminate ventricular fibrillation at high rates in victims of out-of-hospital cardiac arrest. LIFE Investigators. *J Cardiovasc Electrophysiol* 1997; **8**: 1373–85

12 Blouin D, Topping C, Moore S, Snell I, Afilalo M. Out-of-hospital defibrillation with automated external defibrillators: postshock analysis should be delayed. *Ann Emerg Med* 2001; **38**: 256–61

13 Perkins GD, Hulme J, Tweed MJ. Variability in the assessment of advanced life support skills. *Resuscitation* 2001; **50**: 281–6

14 Bartelt KW. Manufacturer's reply. *Br Med J* 1999; **319**: 1574

15 Spearpoint KG, McLean CP, Zideman DA. Early defibrillation and the chain of survival in 'in-hospital' adult cardiac arrest; minutes count. *Resuscitation* 2000; **44**: 165–9

16 Eisenberg MS, Copass MK, Hallstrom A, Cobb LA, Bergner L. Management of out-of-hospital cardiac arrest. Failure of basic emergency medical technician services. *JAMA* 1980; **243**: 1049–51

17 Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 4. the Automated External Defibrillator: Key Link in the Chain of Survival. The American Heart Association in Collaboration with the International Liaison Committee on Resuscitation. *Circulation* 2000; **102** (Suppl 8): 160–76

British Journal of Anaesthesia 89 (3) 409–23 (2002)

Effectiveness of acute postoperative pain management: I. Evidence from published data

S. J. Dolin[1], J. N. Cashman[2]* and J. M. Bland[3]

[1]Pain Clinic, St Richard's Hospital, Chichester PO19 4E, UK. [2]Department of Anaesthesia, St. George's Hospital, London SW17 0QT, UK. [3]Department of Public Health Sciences, St George's Hospital Medical School, London SW17 0RE, UK

**Corresponding author*

Background. This review examines the evidence from published data concerning the incidence of moderate-severe and of severe pain after major surgery, with three analgesic techniques; intramuscular (i.m.) analgesia, patient controlled analgesia (PCA), and epidural analgesia.

Methods. A MEDLINE search of the literature was conducted for publications concerned with the management of postoperative pain. Over 800 original papers and reviews were identified. Of these 212 papers fulfilled the inclusion criteria but only 165 provided usable data on pain intensity and pain relief. Pooled data on pain scores obtained from these studies, which represent the experience of a total of nearly 20 000 patients, form the basis of this review.

Results. Different pain measurement tools provided comparable data. When considering a mixture of three analgesic techniques, the overall mean (95% CI) incidence of moderate-severe pain and of severe pain was 29.7 (26.4–33.0)% and 10.9 (8.4–13.4)%, respectively. The overall mean (95% CI) incidence of poor pain relief and of fair-to-poor pain relief was 3.5 (2.4–4 6)% and 19.4 (16.4–22.3)%, respectively. For i.m. analgesia the incidence of moderate-severe pain was 67.2 (58.1–76.2)% and that of severe pain was 29.1 (18.8–39.4)%. For PCA, the incidence of moderate-severe pain was 35.8 (31.4–40.2)% and that of severe pain was 10.4 (8.0–12.8)%. For epidural analgesia the incidence of moderate-severe pain was 20.9 (17.8–24.0)% and that of severe pain was 7.8 (6.1–9.5)%. The incidence of premature catheter dislodgement was 5.7 (4.0–7.4)%. Over the period 1973–1999 there has been a highly significant ($P<0.0001$) reduction in the incidence of moderate-severe pain of 1.9 (1.1–2.7)% per year.

Conclusions. These results suggest that the UK Audit Commission (1997) proposed standards of care might be unachievable using current analgesic techniques. The data may be useful in setting standards of care for Acute Pain Services.

Br J Anaesth 2002; **89**: 409–23

Keywords: analgesic techniques, intramuscular; analgesia, patient-controlled; anaesthetic techniques, epidural; pain, postoperative

Accepted for publication: April 18, 2002

The Acute Pain Service is a relatively recent innovation, developed to improve the management of postoperative pain.[1] Among the earliest services were those in Kiel[2] and in Seattle.[1] The concept was given impetus in the early 1990s in the UK by the publication of a joint report by the Royal Colleges of Surgeons and Anaesthetists[3] and in USA by the publication of protocol for Investment in Health Gain[4] such that 73% of US hospitals had a pain service by 1994,[5] whilst in the UK 88% of hospitals had an established pain service by 1999.[6]

There is evidence that pain services affect morbidity and duration of hospital stay.[7] However, despite the vast amount published on acute pain there have been few if any attempts to establish standards of care for acute postoperative pain services, although a number of large audits have been published. In a brief reference to postoperative pain in 1997 the Audit Commission (UK) proposed a standard whereby less than 20% of patients should experience severe pain following surgery after 1997, and that this should ideally reduce to less than 5% by 2002.[8] It is not clear from the

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Audit Commission document how these figures have been arrived at, nor how valid this standard might be. In the light of this recommendation we decided to review the published literature on acute pain management in order to establish the validity of the Audit Commission's proposed standard.

In the past, pain relief has been provided mainly by 'as required' intramuscular (i.m.) injections of opioids. More recently, intravenous (i.v.) patient-controlled analgesia (PCA) and epidural analgesia have become popular, as they are perceived as being more effective. However, pain and pain relief are just one aspect of the wide range of outcome variables with which pain services are interest. For a review to be comprehensive it should consider three broad areas of outcome, such as effectiveness, safety, and tolerability. Effectiveness can be inferred from pain scores and pain relief reports. The incidence of respiratory depression and hypotension may be indicative of the safety of the techniques whilst tolerability is reflected by the occurrence of nausea and vomiting, sedation, itching, and the need for urinary catheterization. Psychological effects such as nightmares/hallucinations and panic attacks may also be important.

Methods

Search strategy

We used MEDLINE (1966 onwards) to search the literature for all English language publications concerned with the management of postoperative pain and in particular measures of effectiveness. Keywords selected included analgesia, postoperative pain, pain therapy, i.v. PCA, and epidural analgesia. The computerized search identified keywords in the title, abstract, and medical subject headings (MESH). As standard bibliographic databases label incorrectly nearly 50% of published trials, we also 'hand searched' the full reference lists from review articles and individual relevant papers in peer-reviewed English language journals. Finally, a hand search of four anaesthetic journals (*Anaesthesia*, *British Journal of Anaesthesia*, *Acta Anaesthesiologica Scandinavica*, and *Anesthesiology*) from 1980 to 1999 was performed to cross check the quality of the retrieval method.

All publications identified by the search strategy were categorized according to the level of evidence obtained, based broadly on the criteria of the US Preventive Task Force (Appendix I). Subsequent analysis was not confined to randomized controlled clinical trials but included cohort studies, case control studies, and audit reports; that is level 2 and level 3 evidence. Case reports were not included, nor were authors approached for raw or unpublished data. No attempt was made to grade individual papers according to quality. All of the studies used in the analysis were given equal value. Data extraction was undertaken by one author (S.D.). Figure 1 summarizes the methodology.

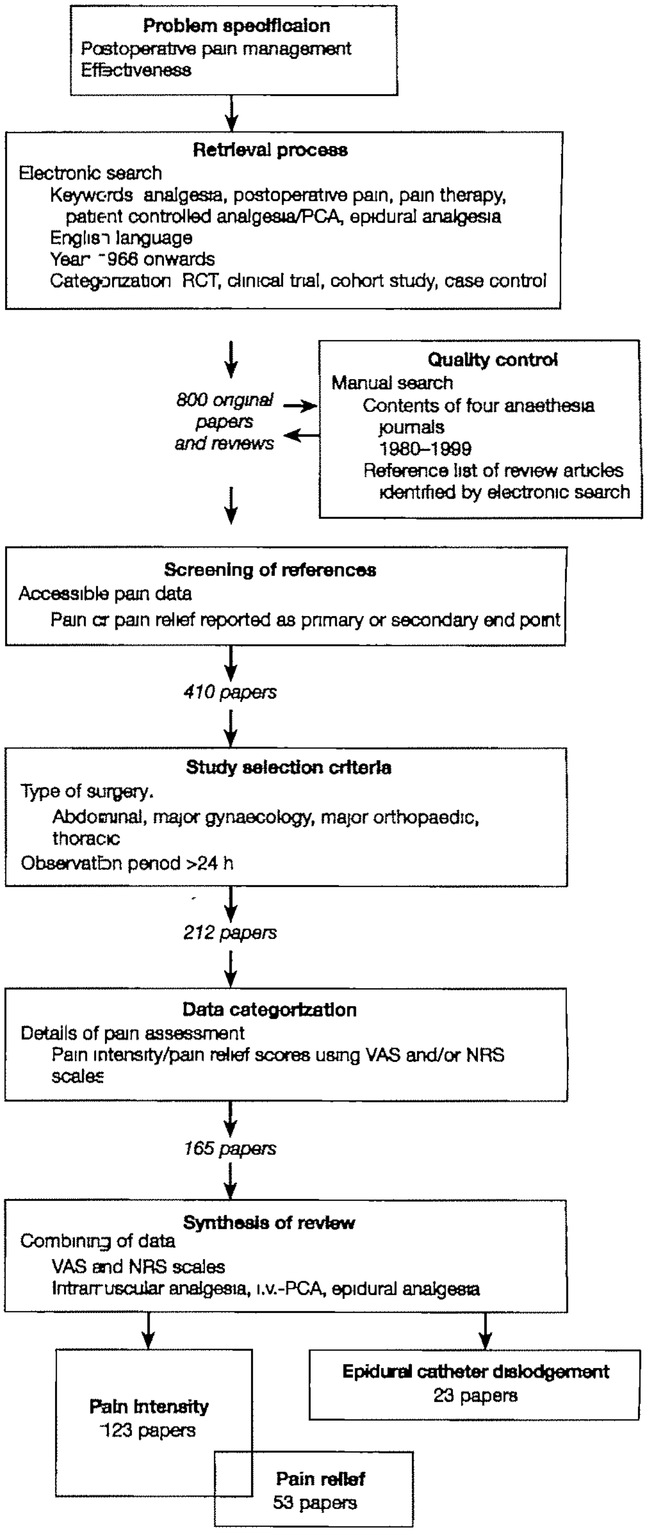

Problem specification
Postoperative pain management
Effectiveness
Retrieval process
Electronic search
Keywords analgesia, postoperative pain, pain therapy, patient controlled analgesia/PCA, epidural analgesia
English language
Year 1966 onwards
Categorization RCT, clinical trial, cohort study, case control
800 original papers and reviews
Quality control
Manual search
Contents of four anaesthesia journals
1980–1999
Reference list of review articles identified by electronic search
Screening of references
Accessible pain data
Pain or pain relief reported as primary or secondary end point
410 papers
Study selection criteria
Type of surgery.
Abdominal, major gynaecology, major orthopaedic, thoracic
Observation period >24 h
212 papers
Data categorization
Details of pain assessment
Pain intensity/pain relief scores using VAS and/or NRS scales
165 papers
Synthesis of review
Combining of data
VAS and NRS scales
Intramuscular analgesia, i.v.-PCA, epidural analgesia
Pain intensity
123 papers
Pain relief
53 papers
Epidural catheter dislodgement
23 papers

Fig 1 Postoperative pain management: data retrieval flow diagram.

Selection criteria

We included articles relating to abdominal, major gynaecological, major orthopaedic, and thoracic surgery. The shortest period of observation was 24 h. Initial observations made in the recovery room were not included. We excluded articles relating to paediatric, day stay, and minor surgery and where the period of observation was less than 24 h. We did not include any study in which a mixed or unusual analgesic technique (e.g. ketamine, clonidine) was described. We did not include articles relating to intrathecal opioids because it is an infrequently used technique (in a Europe-wide survey epidural analgesia was used eight times more frequently than intrathecal analgesia[9]). Neither did we include studies of combined spinal/epidural analgesia nor articles relating to regional analgesic techniques such as interpleural, paravertebral, and lumbar plexus blocks for the same reason.

Definitions

We were interested in obtaining, from the published literature, the incidence of analgesic 'failure' after major surgery. Defining analgesic 'failure' would involve making a number of assumptions, and may differ between patients and medical staff. We have simply calculated the overall incidence of pain intensity in two categories: the percentage of patients who experienced moderate-severe pain and the percentage of patients who experienced severe pain at some time during the first 24 h. We calculated these incidences for each of the three analgesic techniques in common practice: i.m. analgesia, PCA, and epidural analgesia.

Information was extracted from published studies, which reported pain scores using any one of three different measures; visual analogue scale (0–100 mm), numerical rating scale (0–10), and verbal rating scales (mild/moderate/severe). The different measurements have been recorded and where studies involved comparison between drugs using the same technique (e.g. epidural opioids *vs* epidural local anaesthetics) the results have been pooled, to reflect what happens in clinical practice, such as a mixture of drug regimens. Where the study has compared analgesic techniques (PCA *vs* epidural) results have been recorded separately under each technique.

Studies used either contemporaneous pain assessments and/or retrospective pain assessments. For contemporaneous pain scores the worst score in the first 24 h was used, excluding recovery room. The percentage of patients with moderate-severe pain and with severe pain was recorded from each study and this figure was weighted by the number of patients in the study. Moderate-severe pain was taken as a visual score greater than 30/100 or a numerical score greater than 3/10 in this review, in common with most authors. In many but not all studies it was possible to obtain a separate figure for the percentage of patients experiencing severe pain, which was taken as pain intensity score of greater than 70/100 or 7/10. Only when pain intensity scores were reported as raw data, as percentages with moderate or severe pain, or as histograms were we able to extract incidence data. The commonest reason not to include pain intensity data was when pain scores were presented as mean and standard deviation. As the pain scores were unlikely to be normally distributed it was impossible to obtain the percentage of patients experiencing moderate-severe pain and severe pain. Commonly, a single verbal score was recorded after 24 h, whereas visual scores were often recorded contemporaneously at intervals during the 24 h period.

Several studies reported not only pain but also pain relief. Escape criteria such as the need for additional 'rescue' analgesia was also reported in some studies. Most studies reported pain/pain relief at rest but there are some scales that combine pain at rest and on movement; these have been analysed separately.

A number of studies reported the incidence of premature catheter dislodgement, and as this was relevant to analgesic 'failure' this was included in the study. Occasionally the incidence of missed segments or unilateral blocks was reported, but this was insufficient for formal analysis.

Statistics

The mean percentage reporting a given level of pain was found by the method of weighted mean, weighting by the number of subjects in the group.[10] When patients were grouped by analgesic technique, some studies contributed subjects to more than one group. The presence of a few studies in more than one analgesic technique was ignored in the analysis, possibly resulting in a small loss of power. Where appropriate groups were compared using analysis of variance. The percentage of patients reporting pain was weighted by the number as described previously and this figure was used in the analysis rather than any other statistical transformation. This is because our main aim was to estimate the percentage reporting pain for the whole population. All analyses were done using Stata 5.0 (Stata Corp., College Station, TX).

Results

We identified over 800 original papers and reviews, 410 of which contained data that were suitable for the meta-analysis as a whole. Papers which fulfilled our inclusion and exclusion criteria, and from which we were able to extract usable data on pain intensity and pain relief (several papers had data on both) data totalled 212. Some papers contributed both pain intensity and pain relief data. This resulted in 222 papers as follows: i.m. analgesia 45 papers (Appendix II), PCA 73 papers (Appendix III), and epidural analgesia 104 papers (Appendix IV). Pain intensity results were obtained from 123 papers, which included a total of 19 909 patients, published between 1973 and 1999. Pain relief results were obtained from 53 papers, which included 9068 patients published between 1972 and 1998. The incidence of premature epidural catheter dislodgement was obtained from 32 papers, which included 13 629 patients, published between 1975 and 1998 (Appendix V).

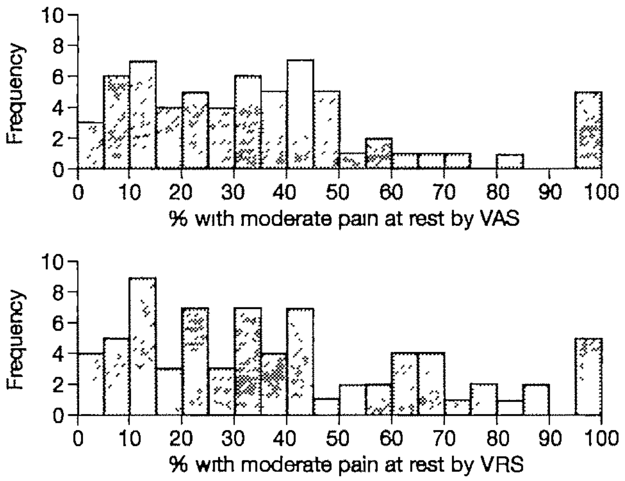


Fig 2 Frequency distribution (numbers of papers) reporting moderate-severe pain at rest as measured by visual and verbal scales There were no differences between these two methods of pain measurement.

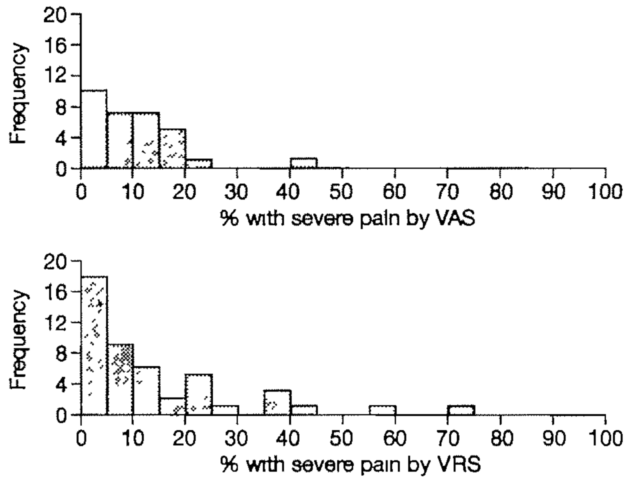


Fig 3 Frequency distribution (numbers of papers) reporting severe pain at rest as measured by visual and verbal scales. There were no differences between these two methods of measuring pain

Pain intensity

We initially analysed visual and verbal scales separately. Visual or verbal scales produced similar distributions for the percentage of patients having moderate or greater pain (Fig. 2). The corresponding distributions for severe pain are shown in Figure 3. Visual and verbal pain scales were compared using analysis of variance and there were no significant differences between the distributions.

Table 1 shows the percentage of patients experiencing moderate-severe and severe pain for both visual and verbal scales, and when both scales were combined. These results were similar for both scales and when considered together with the analysis of the distributions in Figures 2 and 3, we felt that it was statistically valid to regard the distributions of visual and verbal scales as coming from the same population. Subsequent analysis was therefore conducted on the combined data, allowing the maximum possible number of studies to be used.

The overall mean percentages reporting pain in the three analgesic techniques, weighted for study size, are shown in Table 2: the percentage reporting moderate-severe pain at rest is thus estimated to be between 26 and 33%. Severe pain was reported by between 8 and 13% of patients in the first 24 h after major surgery.

As part of the analysis we looked at how the incidence of pain altered between 1973 and 1999. The analgesic technique reported varied with year of publication (Table 3). In the early part of the period of the analysis, i.m. analgesia was the most frequently reported technique, whereas in the later part epidural analgesia was the most frequent. Between 1973 and 1999 there was a significant fall in the overall incidence of moderate-severe pain at rest ($P<0.0001$), by 1.9% per annum (95% CI 1.1–2.7). When the relationship between percentage reporting moderate-severe pain and year of publication was adjusted for analgesic technique, the relationship with time was no longer significant ($P=0.7$) and the estimated fall was reduced to 0.2% per annum (95% CI –0.6 to 0.9). The effect of analgesic technique was highly significant ($P<0.0001$), indicating that as epidural analgesia was introduced postoperative analgesia improved over time.

The incidence of moderate-severe pain and severe pain by analgesic technique is shown in Table 4. Epidural analgesia resulted in the smallest percentage reporting both moderate-severe incidence for pain and severe pain, while i.m. analgesia resulted in the highest percentage. Moderate-severe pain on movement was unreliable, because pain on movement was not commonly reported except in studies of epidural analgesia, with resulting wide confidence intervals. There were no differences between analgesic techniques in the relative numbers of studies based on type of surgery (gynaecological, abdominal, orthopaedic, and thoracic).

Pain relief

Nearly all pain relief was recorded using a verbal rating scale (good, fair, poor) and were generally retrospective, so we have not separated the methods of recording. The results are shown in Table 5.

Overall, between 2 and 5% of patients reported poor pain relief and between 16 and 22% reported only fair-to-poor pain relief. While poor pain relief was most frequently reported by patients receiving epidural analgesia, the numbers of papers was small with wide confidence intervals.

Over the period 1972–1998 significantly fewer patients reported poor pain relief ($P<0.04$), a decrease of 0.4 (95% CI 0.1–0.6) percentage points per year. When adjusted for analgesic technique the relationship was no longer significant. However, the proportion reporting fair-to-poor pain relief was unchanged over time.

Table 1 Percentage of patients reporting moderate-severe pain or severe pain as measured by the three different pain scales, unweighted for study size VAS=visual analogue scale, VRS=verbal rating scale

	Number of studies	Mean (%) reporting pain	Standard deviation	Range	
				Min	Max
VAS pain score only					
Moderate-severe at rest	64	35	26	0	100
Moderate-severe on movement	25	44	31	0	95
Severe	31	9	9	0	44
VRS pain score only					
Moderate-severe at rest	73	39	28	0	100
Moderate-severe on movement	9	38	29	0	78
Severe	47	13	16	0	73
Combined VAS and VRS pain score					
Moderate-severe at rest	136	37	27	0	100
Moderate-severe on movement	33	41	30	0	95
Severe	78	11	14	0	73

Table 2 Percentage of patients reporting moderate-severe pain or severe pain, as measured by all three pain scales combined, weighted for study size VAS=visual analogue scale, VRS=verbal rating scale

Combined VAS and VRS pain score	Number of studies	Mean (%) reporting pain	Standard error	95% Confidence interval
Moderate-severe at rest	136	29.7	1.7	26 4–33 0
Moderate-severe on movement	33	32.2	3.7	24 8–39 6
Severe	78	10 9	1.3	8 4–13 4

Premature epidural catheter dislodgement

We have confined our analysis to the incidence of catheter loss as we felt that unilateral block and missed segment represented technical difficulties with instigating the block. The overall mean (95% CI) incidence of premature epidural catheter dislodgement based on 13 629 patients from 32 studies was 5.7 (4.0–7.4)%.

Table 3 Numbers of published studies by year of publication i m =intramuscular, PCA=patient-controlled analgesia

Publication date	Method of analgesia			Total
	i.m.	PCA	Epidural	
Pre 1974	1	0	0	1
1975–1979	0	1	2	3
1980–1984	5	4	1	10
1985–1989	14	9	18	41
1990–1994	11	19	27	55
1995–1999	0	16	23	39

Discussion

How much pain is acceptable after surgery? The evidence from this review indicates that the overall incidence of severe pain reported in the literature is 11%. This contrasts with the Audit Commission's (UK) recommendation that by 2002 less than 5% of patients should experience severe postoperative pain. However, when considering a standard of care for pain intensity case mix is important. Day surgery pain can result in mild or no pain that can be managed by relatively simple techniques and procedures including take-home oral analgesia and advice.[11] This review was limited to those operations after which moderate-severe post-operative pain could be expected, namely major abdominal gynaecological surgery, major orthopaedic surgery, and any laparotomy or thoracotomy.[12] Importantly, these operations would all be in the remit of the pain service and would generally require postoperative analgesia by i.m. analgesia, PCA, or epidural analgesia.

This review differs from a formal systematic review with meta-analysis in a number of respects. We did not confine ourselves to randomized controlled trials and no attempt was made to grade individual papers according to quality. All of the studies used in the analysis were given equal value as we were not concerned with the conclusion of the individual study merely the incidences of pain intensity We feel that this approach is justified as we were not considering the results of published studies but were concerned with extracting the data from them. However, we did confine our search to English language publication because of the necessity to read in detail both the methods and results sections of each paper. This might be considered as a flaw although the large number of publications included will tend to reduce any tendency to bias. The hand search performed on four anaesthetic journals was designed to cross check the completion of the electronic search. As few new papers were picked up by this search method it was not extended to

Table 4 Percentage of patients reporting moderate-severe pain or severe pain by analgesic technique, weighted for study size *Cannot be estimated as numbers are too small i.m =intramuscular; PCA=patient-controlled analgesia

Analgesic technique	Number of studies	Mean (%) reporting pain	Standard error	95% Confidence interval
Moderate-severe pain at rest				
i.m.	29	67.2	4.4	58.1–76.2
PCA	45	35.8	2.2	31.4–40.2
Epidural	62	20.9	1.6	17.8–24.0
Moderate-severe pain on movement				
i.m.	1	78.0	*	*
PCA	10	25.3	7.5	8.4–42.1
Epidural	22	37.9	3.6	30.4–45.4
Severe pain				
i.m.	21	29.1	4.9	18.8–39.4
PCA	27	10.4	1.2	8.0–12.8
Epidural	30	7.8	0.8	6.1–9.5

Table 5 Percentage of patients reporting fair-to-poor pain relief or poor pain relief by analgesic technique, weighted for study size. *Cannot be estimated as numbers are too small i.m =intramuscular; PCA=patient-controlled analgesia

	Number of studies	Mean (%) reporting pain relief	Standard error	95% Confidence interval
All subjects				
Poor	38	3.5	0.5	2.4–4.6
Fair-to-poor	47	19.4	1.5	16.4–22.3
% reporting poor pain relief				
i.m.	5	1.6	1.3	*
PCA	17	3.6	0.8	1.8–5.4
Epidural	16	5.2	0.7	3.7–6.8
% reporting poor or fair pain relief				
i.m	12	21.3	3.5	13.6–29.1
PCA	16	16.7	2.2	12.1–21.3
Epidural	19	19.4	2.1	15.0–23.7

other journals. Data extraction was undertaken by one author, because we did not need to confer over quality of each study, simply extract reported incidence. A degree of heterogeneity is inevitable in a review of this type. However, we feel that the large numbers of studies included and the small number of differences sought will reduce the likelihood of statistical heterogeneity. Also, we were mindful of the dangers of over interpretation inherent in searching for causes of heterogeneity. Indeed, it has been suggested that over investigating heterogeneity may be likened to subgroup analysis in individual trials.[13] Nevertheless, we have simply reported incidences of pain intensity, and refrained from formal statistical comparisons between analgesic techniques. With respect to clinical heterogeneity we found that the surgical case mix of the studies used was not only very similar between the three analgesic techniques but was also similar to that reported by Moriarty and colleagues[14] and to the case mix of the Acute Pain Service in one of the authors' hospitals (Table 6). We feel confident therefore that these findings mirror 'clinical practice'.

Table 6 Surgical case mix of studies used in review: percent of papers published in each surgical discipline by analgesic technique compared with audit data *Results of St George's Hospital Acute Pain Service audit 1998–1999 (unpublished)

Analgesic technique	Surgical discipline			
	General (%)	Gynaecology (%)	Orthopaedic (%)	Thoracic (%)
i.m	59	13	10	18
PCA	69	17	12	2
Epidural	56	6	11	27
Moriarty *et al.*[14] (*n*=1660)	69	4	14	2
Audit data* (*n*=1571)	34	22	20	13

The evaluation of pain after surgery is complex. It is generally accepted that the visual analogue scale is more sensitive and more accurate in representing pain intensity than other single dimension pain scales. Nevertheless, verbal rating scales (mild/moderate/severe) are widely used clinically and have the advantage of reflecting some of the multidimensional nature of pain. There is evidence that visual and verbal scales are moderately well correlated.[15] Other pain scores such as Magill Pain Questionnaire are rarely used for acute postoperative pain.

Analgesic 'failure' has been described in various terms in different studies depending on which pain scale was used. Many studies using verbal rating scales regarded moderate or severe pain in the postoperative period as representing inadequate analgesia. In studies that have used visual scales, scores more than 30/100 or 3/10, respectively, were the most frequently used scores indicative of inadequate analgesia.[17 18] Rarely lower scores (more than 20/100)[19] or higher scores (more than 50/100)[20] were used as endpoints to define inadequate analgesia. A visual score more than 70/100 was the most common endpoint to define severe pain, although more than 50 has been used.[21] Another group has proposed that moderate pain on verbal score equates to a mean visual score of 49 mm, whilst severe pain equates to a mean visual score of 75 mm.[16] Nevertheless, by analysing both visual and verbal scales separately we were able to demonstrate that, used in this way, these two scoring systems give broadly similar results, and can be used interchangeably.

A number of studies recorded pain both at rest and on movement. It is unclear whether patients distinguish between pain at rest and pain on movement. This may be influenced by such factors as presence of persistent cough, need for physiotherapy, dressing changes, etc. It is probable that, when patients are asked to rate pain over the previous 4 h or at the end of 24 h, they may not distinguish between pain at rest and pain on movement, but may give an overall assessment. It was interesting to note that measurement of pain on movement occurred mostly in studies involving epidural analgesia and seemed of less concern to authors reporting results for other techniques. There were sufficient data to calculate an overall incidence only for pain on movement for moderate-severe pain, but not for severe pain alone. It seems from the literature that pain on movement was reported relatively infrequently and the calculated incidence of pain was associated with wide confidence intervals. For this reason we have limited conclusions and recommendations to pain at rest, which was available for both moderate-severe pain and severe pain, and was associated with narrower confidence intervals.

A number of studies report not only pain intensity but also pain relief. Escape criteria such as the need for additional 'rescue' analgesia have also been reported in some studies. The literature on pain relief after major surgery reports a wide range of effectiveness of analgesic techniques. It was unclear how to interpret the incidence of pain relief, as opposed to pain intensity. There were sufficient studies to calculate incidence of fair-to-poor pain relief and poor pain relief but confidence intervals were relatively wide. The incidences of pain relief do not match the incidences of pain intensity, either overall or for each analgesic technique. It is possible that the incidence of pain intensity is a more direct measure, as pain relief will presumably vary with initial pain intensity.

Our findings that i.m. analgesia was associated with the highest percentage of patients experiencing inadequate analgesia support the general view that it is the least effective of the three techniques studied. Although using strict criteria for administration, i.m. analgesia can be an effective technique,[22 23] the literature suggests this does not occur in clinical practice. The rate of analgesia 'failure' after i.m. analgesia has received relatively scant attention in the literature; there were only 45 published articles (many acting as control groups for other techniques) with no large prospective studies as exist for both PCA and epidural analgesia. Epidural analgesia is generally considered more effective than PCA. Large prospective studies of epidural analgesia such as Scott report 17.4% analgesic failure[22] and Stenseth reported 24–37% of patients after laparotomy experienced analgesic failure by their criteria.[25] Our review indicates a lower incidence of moderate-severe pain and severe pain when epidural was used (20.9 and 7.8%, respectively) compared with PCA (35.8 and 10.4%, respectively). The epidural figures are undoubtedly confounded by technical failures such as premature epidural catheter displacement, which we found to have an incidence of 5.7%. Epidural analgesia does present some particular challenges to pain services. The rate of technical failure has been reported as high as 18.7% in the first 72 h.[25] In addition to premature catheter dislodgement, problems include unsuccessful placement, unilateral block, and missed segments. When these problems occur on postoperative wards there may be no back-up analgesia provided, and it may take time for the problem to be recognized and an appropriate response initiated.

We avoided any measures of patient satisfaction in this review, although some studies did report satisfaction rates. Satisfaction is complex and probably has contributions from many aspects of postoperative care, including effectiveness of analgesia, and perceived safety of analgesic technique and side-effects of treatment. While a number of studies have assessed patient satisfaction and measuring postoperative pain intensity, there was generally a poor correlation between the two. Patient satisfaction remains high even in the presence of moderate to severe pain.[17 26 27] The reasons for this are complex. Patients appear to expect some pain after surgery. Furthermore, in the presence of pain, patients are apparently satisfied by the fact that their health carers are attempting to provide pain relief even if the results are not always successful, as judged by postoperative pain scores. Satisfaction does not actually measure what happened after surgery, but only how satisfied the patient was about what happened. If patients are not aware that excellent postoperative pain relief is achievable then they may well be satisfied with less. Patients may not seek complete pain relief and so self-administer PCA to only moderate levels of pain relief.[28] In addition patients may report higher satisfaction for fear of offending those providing their postoperative care. Measuring patient satisfaction will, it seems, nearly always show high levels of satisfaction for pain relief after surgery, and it is not a particularly discriminating measure of success of a pain service.

In summary, we present a review of published data on the effectiveness of acute postoperative pain management from which it has been possible to calculate the incidence of moderate-severe pain and of severe pain after major surgery for each of the three commonly used analgesic techniques. Assuming a mixture of analgesic techniques the overall incidence of moderate-severe pain was 30% and the overall incidence of severe pain was 11%. For i.m. analgesia the incidence of moderate-severe pain was 67% and that of severe pain was 29%. For PCA, the incidence of moderate-severe pain was 36% and that of severe pain was 10%. For epidural analgesia the incidence of moderate-severe pain was 21% and that of severe pain was 8%. The incidence of premature epidural catheter dislodgement was 6%. These incidences of pain are calculated weighted means and so it is possible to propose reasonable targets. We suggest that individual pain services should aim to achieve figures better than the above mean incidences. However, despite the significant reduction in the incidence of pain over time we would suggest that, based on these data, the UK Audit Commission's standard of less than 5% of patients experiencing severe pain after major surgery by 2002 may not be achievable.

Appendix I

United States Preventive Task Force levels of evidence

Level 1

Evidence obtained from systematic review of relevant randomized controlled trials with meta-analysis where possible (review with secondary data analysis).

Level 2

Evidence from one or more well-designed randomized clinical trial (RCT).

Level 3

Evidence from well-designed, non-controlled studies (prospective longitudinal study with/without specific intervention) or from well-designed case-controlled studies (retrospective study of a cohort with information pursued backwards in time).

Appendix II

References used to obtain incidences of moderate or greater pain—i.m.

Albert JM, Talbott TM. PCA versus conventional intramuscular analgesia following colon surgery. *Dis Colon Rectum* 1988; **31**: 83–6

Atwell JR, Flanigan RC, Bennett RL, Allen DC, Lucas BA, McRoberts JW. The efficacy of patient controlled analgesia in patients recovering from flank incisions. *J Urol* 1984; **132**: 701–3

Austin KL, Stapleton JV, Mather LE. Multiple intramuscular injections: a major source of variability in analgesic response to meperidine. *Pain* 1980, **8**: 47–62

Bennett R, Batenhorst R, Graves DA, Foster TS, Griffen WO, Wright BD. Variation in postoperative analgesic requirements in the morbidly obese following gastric bypass surgery. *Pharmacotherapy* 1982; **2**: 50–3

Bollish SJ, Collins CL, Kirking DM, Bartlett RH. Efficacy of patient controlled versus conventional analgesia for postoperative pain. *Clin Pharm* 1985; **4**: 48–52

Bourke DL, Spatz E, Motara R, Ordia JI, Reed J, Hlavacek JM. Epidural opioids during laminectomy surgery for postoperative pain. *J Clin Anaesth* 1992; **4**: 277–81

Brewington K. PCA in gynecological surgery. *Alabama Med* 1989; **Nov**: 15–17

Brown CR, Mazzulla JP, Mok MS. Nussdorf T, Rubin P, Schwesinger WH. Comparison of repeat doses of intramuscular ketorolac and morphine for analgesia after major surgery. *Pharmacotherapy* 1990; **10**: 45S–49S

Chen PP, Chui PT, Gin T: Comparison of ondansetron and metoclopramide for the prevention of postoperative nausea and vomiting after major gynaecological surgery. *Eur J Anaesthesiol* 1996; **13**: 485–91

Cohen FL. Postsurgical pain relief: patients' status and nurses' medication choices. *Pain* 1980; **9**: 265–74

Cronin M, Redfern PA, Utting JE. Psychometry and post-operative complaints in surgical patients. *Br J Anaesth* 1973; **45**: 879–86

Dahl JB, Daugaard JJ, Larsen HV, Mouridsen P, Nielsen TH, Kristoffersen E. Patient controlled analgesia: a controlled trial. *Acta Anaesthesiol Scand* 1987; **31**: 744–7

Donovan BD. Patient attitudes to postoperative pain relief. *Anaesth Intensive Care* 1983; **11**: 125–8

Eisenach JC, Grice SC, Dewan DM. Patient controlled analgesia following cesarean section; a comparison with epidural and intramuscular narcotics. *Anesthesiology* 1988; **68**: 444–8

Goudie TA, Allan WB, Lonsdale M, Burrow LM, Macrae WA, Grant IS. Continuous subcutaneous infusion of morphine for postoperative pain relief. *Anaesthesia* 1985; **40**: 1086–92

Gurel A, Unal N, Elevli M, Eren A. Epidural morphine for postoperative pain relief in anorectal surgery. *Anesth Analg* 1986; **65**: 459–502

Harrison DH, Sinatra R, Morgese L, Chung JH. Epidural narcotic and PCA for post cesarean section pain relief. *Anesthesiology* 1988; **68**: 454–7

Hasenbos M, van Egmund J, Gielen M, Crul JF. Postoperative analgesia by epidural versus intramuscular nicomorphine after thoracotomy. Part I. *Acta Anaesthesiol Scand* 1985; **29**: 572–6

Hasenbos M, van Egmond J, Gielen M, Crul JF. Postoperative analgesia by epidural versus intramuscular nicomorphine after thoracotomy. Part II. *Acta Anaesthesiol Scand* 1985; **29**: 577–82

Hasenbos M, van Egmond J, Gielen M, Crul JR. Postoperative analgesia by high thoracic epidural versus intramuscular nicomorphine after thoracotomy. *Acta Anaesthesiol Scand* 1987; **31**: 608–15

Hew E, Foster K, Gordon R, Hew-Sang E. A comparison of nalbuphine and meperidine in treatment of postoperative pain. *Can J Anaesth* 1987; **34**: 462–5

Hjortso NC, Neumann P, Frosig F, Andersen T, Lindhard A, Rogon E, Kehlet H. A controlled study on the effect of epidural analgesia with local anaesthetics and morphine on morbidity after abdominal surgery. *Acta Anaesthesiol Scand* 1985; **29**: 790–6

Jayr C, Thomas H, Rey A, Farhat F, Lasser P, Bourgain J. Postoperative pulmonary complications: epidural analgesia using bupivacaine and opioids versus parenteral opioids. *Anesthesiology* 1993; **78**: 666–76

Kalso E, Pertunnen K, Kaasinen S. Pain after thoracic surgery. *Acta Anaesthesiol Scand* 1992; **36**: 96–100

Kenady DE, Wilson JF, Schwartz RW, Bannon CL. A randomised comparison of PCA versus standard analgesic requirements in patients undergoing cholecystetomy. *Surg Gynecol Obstet* 1992, **174**: 216–8

Kilbride MJ, Senagore AJ, Mazier WP, Ferguson C, Ufkes T. Epidural analgesia. *Surg Gynecol Obstet* 1992; **174**: 137–40

Kuhn S, Cooke K, Collins M, Jones JM, Mucklow JC. Perceptions of pain relief after surgery *BMJ* 1990; **300**: 1687–90

Lange MP, Dahn MS, Jacobs LA. PCA versus intermittent analgesia dosing *Heart Lung* 1988; **17**: 495–8

Langford R, Bakhshi K, Moylan S, Foster JM. Hypoxaemia after lower abdominal surgery: comparison of tramadol and morphine. *Acute Pain* 1998; **1**: 7–12

Logas WG, el-Baz N, el-Ganzouri A, *et al.* Continuous thoracic epidural analgesia for postoperative pain relief following thoracotomy. *Anesthesiology* 1987; **67**: 787–91

Mahoney OM, Noble PC, Davidson J, Tullos HS. The effect of continuous epidural analgesia on postoperative pain, rehabilitation and duration of hospitalisation in total knee arthroplasty. *Clin Orthop Related Res* 1990; **260**: 30–7

Nimmo WS, Todd JG Fentanyl by constant rate intravenous infusion for postoperative analgesia. *Br J Anaesth* 1985; **57**. 250–4

Owen H, McMillan V, Rogowski D. Postoperative pain therapy: a survey of patients' expectations and their experiences. *Pain* 1990, **41**: 303–7

Powell H, Smallman JM, Morgan M. Comparison of intramuscular ketorolac and morphine in pain control after laparotomy. *Anaesthesia* 1990; **45**, 538–42

Power I, Noble DW, Douglas E, Spence AA. Comparison of intramuscular ketorolac and morphine for pain relief after cholecystectomy. *Br J Anaesth* 1990; **65**. 448–55

Raj PP, Knarr DC, Vigdorth E *et al.* Comparison of continuous infusion of a local anaesthetic and administration of systemic narcotics in the management of pain after total knee replacement surgery *Anesth Analg* 1987; **66**: 401–406

Rawal N, Sjostrand U, Christoffersson E, Dahlstrom B, Arvill A, Rydman H. Comparison of intramuscular and epidural morphine for postoperative analgesia in the grossly obese. *Anesth Analg* 1984; **63**: 583–92

Rosenberg PH, Heino A, Scheinin B. Comparison of intramuscular analgesia, intercostal block, epidural morphine and on-demand intravenous fentanyl in the control of pain after upper abdominal surgery. *Acta Anaesthesiol Scand* 1984; **28**: 603–7

Searle NR, Roy M, Bergeron G, *et al.* Hydromorphone PCA after coronary artery bypass surgery. *Can J Anaesth* 1994; **41**. 198–205

Smythe MA, Zak MB, O'Donnell MP, Schad RF, Dmuchowski CF. Patient controlled analgesia versus PCA plus continuous infusion after hip replacement. *Ann Pharmacother* 1996; **30**: 224–7

Stahlgren L, Trierweiler M, Tommeraasen M, *et al.* Comparison of ketorolac and meperidine in patients with postoperative pain—impact in health care utilization. *Clin Ther* 1993; **15**: 571–81

Tsui SL, Chan CS, Chan AS, Wong SJ, Lam CS, Jones RD. Postoperative analgesia for oesophageal surgery. a comparison of three analgesic regimens. *Anaesth Intensive Care* 1991; **19**: 329–37

Tsui SL, Lo RJ, Tong WN, *et al.* A clinical audit for postoperative pain control on 1443 surgical patients. *Acta Anaesthesiol Sin* 1995, **33**. 137–48

Vijayan R. Subcutaneous morphine—a simple technique for postoperative analgesia. *Acute Pain* 1997; **1**: 21–6

Appendix III

References used to obtain incidences of moderate or greater pain—PCA

Albert JM, Talbott TM. PCA versus conventional intramuscular analgesia following colon surgery *Dis Colon Rectum* 1988, **31**: 83–6

Atwell JR, Flanigan RC, Bennett RL, Allen DC, Lucas BA, McRoberts JW The efficacy of patient controlled analgesia in patients recovering from flank incisions. *J Urol* 1984, **132**. 701–3

Badner NH, Doyle JA, Smith MH, Herrick IA Effect of varying intravenous PCA dose and lockout interval while maintaining a constant hourly maximum dose *J Clin Anesth* 1996; **8**: 382–5

Bahar M, Rosen M, Vickers MD Self-administered nalbuphine, morphine and pethidine. *Anaesthesia* 1985; **40**· 529–32

Bennett RL, Batenhorst RL, Bivins BA, *et al.* PCA. a new concept of postoperative pain relief. *Ann Surg* 1982; **195**: 700–4

Bennett RL, Batenhorst RL, Graves DA, Foster TS, Griffen WO, Wright BD. Variation in postoperative analgesic requirements in the morbidly obese following gastric bypass surgery. *Pharmacotherapy* 1982; **2**: 50–3

Black AM, Goodman NW, Bullingham RE, Lloyd J. Intramuscular ketorolac and morphine during PCA after hysterectomy. *Eur J Anaesthesiol* 1990; **7**: 9–17

Blackburn A, Stevens JD, Wheatley RG, Madej TH, Hunter D. Balanced analgesia with intravenous kerorolac and PCA morphine following abdominal surgery. *J Clin Anaesth* 1995, **7** 103–8

Bollish SJ, Collins CL, Kirking DM, Bartlett RH. Efficacy of patient controlled versus conventional analgesia for postoperative pain *Clin Pharm* 1985; **4**· 48–52

Cepeda MS, Vargas L, Ortegan G, Samnchez MA, Carr DB. Comparative analgesic efficacy of patient controlled analgesia with ketorolac versus morphine after elective intra-abdominal operations. *Anesth Analg* 1995; **80**: 1150–3

Chauvin M, Hongnat JM, Mourgeon E, Lebrault C, Bellanfant F, Alfonsi P. Equivalence of postoperative analgesia with patient controlled intravenous or epidural alfentanil *Anesth Analg* 1993; **76**: 1251–8

Coleman SA, Brooker-Milburn J. Audit of postoperative pain control. *Anaesthesia* 1996; **51**: 1093–6

Dahl JB, Daugaard JJ, Larsen HV, Nielsen TH, Kristoffersen E. Patient controlled analgesia: a controlled trial. *Acta Anaesthesiol Scand* 1987; **31**: 744–7

Dawson PJ, Libreri FC, Jones DJ, Libreri G, Borkstein AR, Royse CF The efficacy of adding a continuous intravenous morphine infusion to patient controlled analgesia in abdominal surgery. *Anaesth Intensive Care* 1995, **23**: 453–8

Dingus DJ, Sherman JC, Rogers DA, DiPiro JT, May R, Bowden TA Buprenorphine versus morphine for PCA after cholecystectomy *Surg Gynecol Obstet* 1993; **177**: 1–6

Eisenach JC, Grice SC, Dewan DM. Patient controlled analgesia following cesarean section, a comparison with epidural and intramuscular narcotics *Anesthesiology* 1988; **68**· 444–8

Etches RC, Warrner CB, Badner N, *et al* Continuous intravenous administration of ketorolac reduces pain and morphine consumption after total hip and knee arthroplasty *Anesth Analg* 1995; **81**: 1175–80

Gallion HH, Wermeling DP, Foster TS, VanNagell JR, Donaldson ES PCA in gynaecologic oncology *Gynecol Oncol* 1987, **27** 247–52

George KA, Wright PM, Chisakuta A, *et al.* Thoracic epidural analgesia compared with patient controlled intravenous morphine after upper abdominal surgery. *Acta Anaesthesiol Scand* 1994; **38**: 808–12

Gilliland HE, Prasad BK, Mirakhur RK, Fee JP. An investigation of the potential morphine sparing effect of midazolam. *Anaesthesia* 1996; **51**: 808–11

Hansen LE, Noyes MA, Lehman ME. Evaluation of PCA versus PCA plus continuous infusion in postoperative cancer patients. *J Pain Symptom Manage* 1991; **6**: 4–14

Harmer M, Slattery P, Rosen M, Vickers MD. Intramuscular on demand analgesia: double blind controlled trial of pethidine, buprenorphine, morphine and meptazinol. *Br J Anaesth* 1983; **286**: 680–2

Harrison DM, Sinatra R, Morgese L, Chung JH. Epidural narcotic and PCA for post-cesarean section pain relief. *Anesthesiology* 1988, **68**: 454–7

Jayr C, Beaussier M, Gustafsson Y, *et al.* Continuous epidual infusion of ropivacaine for postoperative analgesia after abdominal surgery. *Br J Anaesth* 1998; **81**: 887–92

Kenady DE, Wilson JF, Schwartz RW. Bannon CL. A randomised comparison of PCA versus standard analgesic requirements in patients undergoing cholecystetomy *Surg Gynecol Obstet* 1992; **174**· 216–8

Kilbride MJ, Senagore AJ, Mazier WP, Ferguson C, Ufkes T. Epidural analgesia. *Surg Gynecol Obstet* 1992; **174**: 137–40

Klasen JA, Opitz SA, Melzer C, Thiel A, Hempelmann G. Intrarticular, epidural and intravenous analgesia after total knee arthoplasty. *Acta Anaesthesiol Scand* 1999; **43**: 1021–6

deKock MF, Pinchon GP, Scholtes JL. Intraoperative clonidine enhances postoperative morphine PCA. *Can J Anaesth* 1992; **39**: 537–44

van Lancker P, Mortier E, Pieters A, Rolly G. Evaluation of morphine for PCA with the infusorsystem after opiate free locoregional anesthesia for osteotomy of the foot. *Acta Anaesthesiol Belgica* 1995; **46**: 113–9

Lange MP, Dahn MS, Jacobs LA. PCA versus intermittent analgesia dosing. *Heart Lung* 1988; **17**: 495–8

Lehmann KA, Kratzenberg U, Schroeder-Bark B, Horrichs-Haermeyer G. Postoperative PCA with tramadol. analgesic efficacy and minimum effective concentrations. *Clin J Pain* 1990; **6**: 212–20

Lehmann KA, Ribbert N, Horrichs-Haermeyer G Postoperative PCA with alfentanil: anlgesic efficacy and minimum effective concentrations. *J Pain Symptom Manage* 1990; **5**: 249–58

Lehmann KA, Gerhard A, Horrichs-Haermeyer G, Grond S, Zech D. Postoperative PCA with sufentanil: analgesic efficacy and minimum effective concentrations. *Acta Anaesthesiol Scand* 1991; **35**: 221–6

de Leon-Casasola O, Lema MJ, Karabella D, Harrison P. Postoperative myocardial ischaemia: epidural v intravenous PCA. *Reg Anesth* 1995; **20**: 105–12

Loper KA, Ready LB, Nessly M, Rapp SE. Epidural morphine provides greater pain relief than PCA intravenous morphine following cholecystectomy. *Anesth Analg* 1989; **69**: 826–8

Loper KA, Ready LB, Downey M, *et al* Epidural and intravenous fentanyl infusions are clinically equivalent after knee surgery. *Anesth Analg* 1990; **70**: 72–5

Lopez-Olaondo L, Carrascosa F, Pueyo FJ, Monedero P, Busto N, Saez A. Combination of ondansteron and dexamethasone in the prophylaxis of postoperative nausea and vomiting. *Br J Anaesth* 1996; **76**: 835–40

McKenzie R, Rudy T, Ponter-Hammill M. Side effects of morphine PCA and meperidine PCA: a follow-up of 500 patients. *J Am Assoc Nurse Anesth* 1992; **60**: 282–7

van den Nieuwenhuyzen MC, Engbers FH, Burm AG, Vletter AA, van Kleef JW, Bovill JG. Computer controlled infusion of alfentanil versus patient controlled administration of morphine for postoperative analgesia. a double blind randomised trial. *Anesth Analg* 1995; **81**: 671–9

Notcutt WG, Morgan RJ. Introducing patient-controlled analgesia for postoperative pain control into a district general hospital. *Anaesthesia* 1990; **45**: 401–6

Owen H, Plummer JL, Armstrong I, Mather LE, Cousins MJ. Variables of PCA 1: bolus size. *Anaesthesia* 1989, **44**: 7–10

Owen H, Currie JC, Plummer JL. Variation in the blood concentration/analgesic response relationship during PCA with fentanyl. *Anaesth Intensive Care* 1991; **19**: 555–60

Parker RK, Holtmann B, White PF. PCA: does concurrent opioid infusion improve pain management after surgery. *JAMA* 1991; **266**: 1947–52

Persson K, Sjostrom S, Sigurdartdottir I. Patient controlled analgesia with codeine for postoperative pain relief in ten extensive metabolisers and one poor metaboliser of dextromethorphan. *Br J Clin Pharmacol* 1995; **39**: 182–6

Pryle BJ, Vanner RG, Enriquez N, Reynolds F. Can pre-emptive lumbar epidural blockade reduce postoperative pain following lower abdominal surgery. *Anaesthesia* 1993; **48**: 120–3

Pueyo FJ, Carrascosa F, Lopez L, Iribarren MJ, Garcia-Pedrajas F, Saez A. Combination of ondasetron and droperidol in the prophylaxis of postoperative nausea and vomiting. *Anesth Analg* 1996; **83**: 117–22

Robinson SL, Rowbotham DJ, Mushambi M. Electronic and disposable PCA systems. *Anaesthesia* 1992; **47**: 161–3

Rosenberg PH, Heino A, Scheinin B. Comparison of IM analgesia, intercostal block, epidural morphine and on-demand intravenous fentanyl in the control of pain after upper abdominal surgery. *Acta Anaesthesiol Scand* 1984; **28**· 603–7

Russell AW, Owen H, Ilsley AH, Kluger MT, Plummer JL. Background infusion with patient controlled analgesia: effect on postoperative oxyhaemoghlobin saturation and pain control. *Anaesth Intensive Care* 1993; **21**: 174–9

Sands RP, de Leon-Casasola OA, Harrison P, Velagapudi S, Lema MJ. Randomised double blind comparison of epidural and intravenous fentanyl for postoperative pain. *Acute Pain* 1997; **1**: 7–14

Sawaki Y, Parker RK, White PF. Patient and nurse evaluation of PCA delivery systems for postoperative pain management. *J Pain Symptom Manage* 1992; **7**: 443–53

Schug SA, Fry RA. Continuous regional analgesia in comparison with intravenous opioid administration for routine postoperative pain control. *Anaesthesia* 1994; **49**: 528–32

Scott DA, Chamley DM, Mooney PH, Deam RK, Mark AH, Hagglof B. Epidural ropivacaine infusion for postoperative analgesia after major lower abdominal surgery—a dose finding study. *Anesth Analg* 1995; **81**: 982–6

Searle NR, Roy M, Bergeron G, *et al.* Hydromorphone PCA after coronary artery bypass surgery. *Can J Anaesth* 1994; **41**: 198–205

Sharma SK, Davies MW. Patient controlled analgesia with a mixture of morphine and droperidol. *Br J Anaesth* 1993; **71**: 435–6

Shipton EA, Beeton AG, Minkowitz HS. Introducing a PCA based Acute Pain relief service into southern Africa—the first 10 months. *SAMJ* 1993; **83**: 501–55

Sidebotham D, Dijkhuizen MR, Schug SA. The safety and utilization of patient controlled analgesia. *J Pain Symptom Manage* 1997; **14**: 202–9

Smythe M, Loughlin K, Schad RF, Lucarroti RL. PCA versus intramuscular analgesic therapy. *Am J Hosp Pharm* 1994; **51**: 1433–41

Stanley G, Appadu B, Mead M, Rowbotham DJ. Dose requirements, efficacy and side effects of morphine and pethidine by patient controlled analgesia after gynaecological surgery. *Br J Anaesth* 1996; **76**: 484–6

Tamsen A, Hartvig P, Dahlstrom B, Lindstrom B, Holmdahl H. Patient controlled analgesic therapy in the early postoperative period. *Acta Anaesthesiol Scand* 1979; **23**: 462–70

Tamsen A, Hartvig P, Faherlund G, Dahlstrom B, Bondesson U. Patient controlled analgesic therapy: clinical experience. *Acta Anaesthesiol Scand* 1982; **74**: 157–60

Taylor NM, Hall GM, Salmon P. Patients' experiences of patient-controlled analgesia. *Anaesthesia* 1996; **51**: 525–8

Tsui SL, Lo RJ, Tong W, *et al.* A clinical audit for postoperative pain control on 1443 surgical patients. *Acta Anaesthesiol Sin* 1995; **33**: 137–48

Tsui SL, Tong WN, Irwin M *et al.* The efficacy, applicability and side effects of postoperative intravenous patient controlled morphine analgesia: an audit of 1233 Chinese patients. *Anaesth Intensive Care* 1996; **24**· 658–64

Tsui SL, Lee DK, Ng KF, Chan TY, Chan WS, Lo JW. Epidural infusion of bupivacaine plus fentanyl provides better postoperative analgesia than patient controlled analgesia with intravenous morphine after gynaecological laparotomy. *Anaesth Intensive Care* 1997, **25**: 476–81

Upton PM, Beeton AG, Minkowitz HS, Shipton EA. PCA· its South African debut in a provincial hospital. *SAMJ* 1992; **81**: 74–6

Watts RW, Fletcher IA, Kiroff GK, Weber C, Owen H, Plummer JL. The introduction of PCA into isolated rural hospital. *Aust NZ J Surg* 1995; **65**· 588–91

Wermeling DP, Greene SA, Boucher BA *et al.* Multicenter evaluation of PCA device for the treatment of postoperative pain. *Clin Pharm* 1992; **11**: 342–6

Wheatley RG, Madej TH, Jackson IJ, Hunter D. The first year's experience of an acute pain service. *Br J Anaesth* 1991; **67**· 353–9

White WD, Pearce DJ, Norman J. Postoperative analgesia: a comparison of intravenous on-demand fentanyl with epidural bupivacaine. *BMJ* 1979; **2**· 166–7

White PF. Subcutaneous PCA. an alternative to intravenous PCA for postoperative pain management. *Clin J Pain* 1990; **6**: 297–300

Wong LT, Koh LH, Kaur K, Boey SK. A two-year experience of an acute pain service in Singapore *Singapore Med J* 1997, **38**: 209–13

Zacharias M, Pfeifer MV, Herbison P. Comparison of two methods of intravenous administration of morphine for postoperative pain relief. *Anaesth Intensive Care* 1990; **18**· 205–9

Appendix IV

References used to obtain incidences of moderate or greater pain—epidural

Asantila R, Rosenberg PH, Scheinin B. Comparison of different methods of postoperative analgesia after thoracotomy. *Acta Anaesthesiol Scand* 1986; **30**· 421–5

Bailey PW, Smith BE. Continuous epidural infusion of fentanyl for postoperative analgesia. *Anaesthesia* 1980; **35**: 1002–6

Baker MW, Tullos HS, Bryan WJ, Oxspring H. The use of epidural morphine in patients undergoing total knee arthroplasty. *J Arthroplasty* 1989; **4**: 157–9

Banning AM, Schmidt JF, Chraemmer-Jorgensen B, Risbo A. Comparison of oral controlled release morphine and epidural morphine in the management of postoperative pain. *Anesth Analg* 1986, **65**: 385–8

el-Baz N, Goldin M. Continuous epidural infusion of morphine for pain relief after cardiac operations. *J Thorac Cardiovasc Surg* 1987; **93**: 878–83

Bisgaard C, Mouridsen P, Dahl J. Continuous lumbar epidural bupivacaine plus morphine v. epidural morphine after major abdominal surgery. *Eur J Anaesthesiol* 1990; **7** 219–25

Brodsky JB, Chaplan SR, Brose WG, Mark JB. Continuous epidural hydromorphone for postthoracotomy pain relief. *Ann Thor Surg* 1990; **50**: 888–93

Broekema AA, Gielen MJ, Hennis PJ. Postoperative analgesia with continuous epidural sufentanil and bupivacaine. *Anesth Analg* 1996; **82**. 754–9

Burstal R, Wegener F, Hayes C, Lantry G Epidural analgesia: prospective audit of 1062 patients. *Anaesth Intensive Care* 1998; **26**: 165–72

Cahill J, Murphy D, O'Brien D, Mulhall J, Fitzpatrick G. Epidural buprenorphine for pain relief after major abdominal surgery. *Anaesthesia* 1983; **38**: 760–4

Callesen T, Scouenberg L, Nielsen D, Guldager H, Kehlet H. Combined epidural-spinal opioid free anaethesia and analgesia for hysterectomy. *Br J Anaesth* 1999; **82**: 885–88

Capdevila X, Barthelet Y, Biboulet P, Ryckwaert Y, Rubenovitch J, d'Athis F. Effects of perioperative analgesic technique on the surgical outcome and duration of rehabilitation after major knee surgery. *Anesthesiology* 1999; **91**: 8–15

Chaplan S, Duncan S, Brodsky J, Brose W. Morphine and hydromorphone epidural analgesia. *Anesthesiology* 1992; **77**· 1090–4

Chauvin M, Hongnat JM, Mourgeon E, Lebrault C, Bellenfant F, Alfonsi P. Equivalence of postoperative analgesia with patient controlled intravenous or epidural alfentanil. *Anesth Analg* 1993, **76** 1251–8

Chisakuta AM, George KA, Hawthorne CT. Postoperative epidural infusion of a mixture of bupivacaine with fentanyl for upper abdominal surgery. *Anaesthesia* 1995, **50**: 72–5

Chrubasik J, Wiemers K. Continuous plus on demand epidural infusion of morphine for postoperative pain relief by means of a small externally worn infusion device *Anesthesiology* 1985, **62**: 263–7

Coleman SA, Brooker-Milburn J. Audit of postoperative pain control *Anaesthesia* 1996; **51**. 1093–6

Conacher I, Paes M, Jacobsen L, Phillips P, Heaviside D Epidural analgesia following thoracic surgery. *Anaesthesia* 1983, **38**. 546–51

Cox CR, Serpell MG, Bannister J, Coventry DM, Williams DR A comparison of epidural infusions of fentanyl or pethidine with bupivacaine in the management of postoperative pain *Anaesthesia* 1996; **51**: 695–8

Cullen M, Staren E, El-Ganzouri, Logas W, Ivankovich A, Economou S. Continuous epidural infusion for analgesia after major abdominal operations. *Surgery* 1985; **98**: 718–26

Dahl JB, Hansen BL, Hjortso NC, Erichsen CJ, Moiniche S, Kehlet H. Influence of timing on the effect of continuous extradural analgesia with bupivacaine and morphine after major abdominal surgery. *Br J Anaesth* 1992; **69**: 4–8

Duncan LA, Fried MJ, Lee A, Wildsmith JA. Comparison of continuous and intermittent adminstration of extradural bupivacaine for analgesia after lower abdominal surgery. *Br J Anaesth* 1998; **80**. 7–10

Eisenach JC, Grice SC, Dewan DM. Patient controlled analgesia following cesarean section; a comparison with epidural and intramuscular narcotics. *Anesthesiology* 1988; **68** 444–8

Etches RC, Sandler AN, Lawson SL A comparison of the analgesic and respiratory effects of epidural nalbuphine or morphine in post-thoracotomy patients *Anesthesiology* 1991; **75**· 9–14

Fromme GA, Steidl LJ, Danielson DR Comparison of lumbar and thoracic morphine for relief of postthoracotomy pain. *Anesth Analg* 1985; **64**: 454–5

George KA, Wright PM, Chisakuta A. Continuous epidural fentanyl for post-thoracotomy pain relief. *Anaesthesia* 1991; **46**: 732–6

George KA, Chisakuta AM, Gamble JA, Browne GA. Thoracic epidural infusion for postoperative pain relief following abdominal aortic surgery. *Anaesthesia* 1992; **47**: 388–94

George KA, Wright PM, Chisakuta AM, Rao NV. Thoracic epidural analgesia compared with patient controlled intravenous morphine after upper abdominal surgery. *Acta Anaesthesiol Scand* 1994; **38**: 808–12

Griffiths DP, Diamond AW, Cameron JD. Postoperative extradural analgesia following thoracic surgery: a feasibility study. *Br J Anaesth* 1975; **47**: 48–54

Gundersen RY, Andersen R, Narverud G. Postoperative pain relief with high dose epidural buprenorphine: a double blind study. *Acta Anaesthesiol Scand* 1986; **30**: 664–7

Hansdottir V, Bake B, Nordberg G. The analgesic efficacy and adverse effects of continuous epidural sufentanil and bupivacaine infusion after thoracotomy. *Anesth Analg* 1996; **83**: 394–400

Harbers JB, Hasenbos MA, Gort C, Folgering H, Dirksen R, Gielen MJ. Ventilatory function and continuous high thoracic epidural administration of bupivacaine with sufentanil intravenously or epidurally: a double blind comparison. *Reg Anesth* 1991; **16**. 65–71

Harrison DM, Sinatra R, Morgese L, Chung JH. Epidural narcotic and PCA for post-cesarean section pain relief. *Anesthesiology* 1988, **68**: 454–7

Hasenbos M, Van Egmond J, Gielen M, Crul JF. Postoperative analgesia by epidural versus intramuscular nicomorphine after thoracotomy. Part II. *Acta Anaesthesiol Scand* 1985; **29**: 577–82

Hasenbos M, van Egmond J, Gielen M, Crul JF. Postoperative analgesia by high thoracic epidural versus intramuscular nicomorphine after thoracotomy. *Acta Anaesthesiol Scand* 1987; **31**: 608–15

Hjortso NC, Neumann P, Frosig F, *et al* A controlled study on the effect of epidural analgesia with local anaesthetics and morphine on morbidity after abdominal surgery. *Acta Anaesthesiol Scand* 1985; **29**: 790–6

Hjortso NC, Lund C, Mogensen T, Bigler D, Kehlet H. Epidural morphine improves pain relief and maintains sensory analgesia during continuous epidural bupivacaine after abdominal surgery. *Anesth Analg* 1986; **65**: 1033–6

Hobbs GJ, Roberts FL. Epidural infusion of bupivacaine and diamorphine for postoperative analgesia: use on general surgical wards. *Anaesthesia* 1992; **47**: 58–62

Holmdahl MH, Sjogren S, Strom G, Wright B. Clinical aspects of continuous epidural blockade for postoperative pain relief. *Upsala Med J* 1972; **77**: 47–56

Hurford WE, Dutton RP, Alfille PH, Clement D, Wilson RS. Comparison of thoracic and lumbar epidural infusions of bupivacaine and fentanyl for postthoracotomy analgesia. *J Cardiothorac Vasc Anaesth* 1993; **7**: 521–5

Jayr C, Thomas H, Rey A, Farhat F, Lasser P, Bourgain JL. Postoperative pulmonary complications: epidural analgesia using bupivacaine and opioids v. parenteral opioids. *Anesthesiology* 1993, **78**: 666–76

Jayr C, Beaussier M, Gustafsson Y, *et al*. Continuous epidual infusion of ropivacaine for postoperative analgesia after abdominal surgery. *Br J Anaesth* 1998; **81**: 887–92

Kilbride MJ, Senagore AJ, Mazier WP, Ferguson C, Ufkes T. Epidural analgesia. *Surg Gynecol Obstet* 1992; **174**: 137–40

Klasen JA, Opitz SA, Melzer C, Thiel A, Hempelmann G. Intraarticular, epidural and intravenous analgesia after total knee arthroplasty. *Acta Anaesthesiol Scand* 1999; **43**: 1021–6

de Kock M, Gautier P, Pavlopolou A, Jonniaux M, Lavand'homme P. Epidural clonidine or bupivacaine as the sole analgesic agent during and after abdominal clonidine. *Anesthesiology* 1999; **90**: 1354–62

Larsen VH, Iversen AD, Christensen P, Andersen PK. Postoperative pain treatments after upper abdominal surgery with epidural morphine at thoracic or lumbar level. *Acta Anaesthesiol Scand* 1985; **29**: 566–71

Laveaux MM, Hasenbos MA, Harbers JB, Liem T. Thoracic epidural bupivacaine plus sufentanil: high concentration/low volume versus low concentration/high volume. *Reg Anaesth* 1993; **18**: 39–43

Lee A, Simpson D, Whitfield A, Scott D. Postoperative analgesia by continuous extradural infusion of bupivacaine and diamorphine. *Br J Anaesth* 1988; **60**: 845–50

Leith S, Wheatley RG, Jackson IJ, Madej TH, Hunter D. Extradural infusion analgesia for postoperative pain relief. *Br J Anaesth* 1994; **73**: 552–8

de Leon-Casasola OA, Lema MJ, Karabella D, Harrison P. Postoperative myocardial ischaemia: epidural versus intravenous PCA. *Reg Anesth* 1995; **20**: 105–12

Logas WG, el-Baz N, el-Ganzouri A, *et al*. Continuous thoracic epidural analgesia for postoperative pain relief following thoracotomy. *Anesthesiology* 1987; **67**: 787–91

Loper KA, Ready LB. Epidural morphine after anterior cruciate ligament repair: a comparison with patient-controlled intravenous morphine. *Anesth Analg* 1989; **68**: 350–2

Loper KA, Ready LB, Nessly M, Rapp SE. Epidural morphine provides greater pain relief than PCA intravenous following cholecystectomy *Anesth Analg* 1989; **69**: 826–8

Loper KA, Ready LB, Downey M, *et al*. Epidural and intravenous fentanyl infusions are clinically equivalent after knee surgery. *Anesth Analg* 1990; **70**: 72–5

Lubenow TR, Faber LP, McCarthy RJ, Hopkins EM, Warren WH, Ivankovitch AD. Post-thoracotomy pain management using continuous epidural analgesia in 1324 patients. *Ann Thorac Surg* 1994; **58**: 924–30

Lubenow TR, Tanck EN, Hopkins EM, *et al*. Comparison of patient assisted epidural analgesia with continuous epidural analgesia for postoperative patients. *Reg Anesthesia* 1994; **19**. 206–11

Magora F, Olshwang D, Eimerl D, *et al*. Observations on extradural morphine analgesia in various pain conditions. *Br J Anaesth* 1980; **52**: 247–52

Mahoney OM, Noble PC, Davidson J, Tullos HS. The effect of continuous epidural analgesia on postoperative pain, rehabilitation and duration of hospitalisation in total knee arthroplasty. *Clin Orthopaed Related Res* 1990; **260**: 30–7

Marlowe S, Engstrom R, White PF. Epidural PCA: an alternative to continuous epidural infusions. *Pain* 1989; **37**: 97–101

Mehnert JH, Dupont TJ, Rose DH. Intermittent epidural morphine instillation for control of postoperative pain. *Am J Surg* 1983; **146**. 145–51

Mehta Y, Juneja R, Madhok H, Trehan N. Lumbar versus thoracic epidural buprenorphine for postoperative analgesia following coronary artery bypass graft surgery. *Acta Anaesthesiol Scand* 1999, **43**: 388–93

Mogensen T, Hjörtso NC, Bigler D, Lund C, Kehlet H. Unpredictability of regression of analgesia during the continuous postoperative extradural infusion of bupivacaine. *Br J Anaesth* 1988; **60**: 515–9

Mourisse J, Hasenbos MA, Gielen MJ, Moll JE, Cromheecke GJ. Epidural bupivacaine, sufentanil or the combination for post-thoracotomy pain. *Acta Anaesthesiol Scand* 1992; **36**: 70–4

Muldoon T, Milligan K, Quinn P, Connolly DC, Nilsson K. Comparison between extradural infusion of ropivacaine or bupivacaine for the prevention of postoperative pain after total knee replacement. *Br J Anaesth* 1998; **80**: 680–1

Nolan J, Dow A, Parr M, *et al.* Patient controlled epidural analgesia following post-traumatic pelvic reconstruction. *Anaesthesia* 1992; **47**: 1037–41

Owen H, Kluger MT, Ilsley AH, Baldwin AM, Fronsko RR, Plummer JL. The effect of fentanyl administered epidurally by patient controlled analgesia, continuous infusion, or a combined technique of oxyhaemoglobin saturation after abdominal surgery. *Anaesthesia* 1993; **48**· 20–5

Raj PP, Knarr DC, Vigdorth E, *et al.* Comparison of continuous infusion of a local anaesthetic and administration of systemic narcotics in the management of pain after total knee replacement surgery. *Anesth Analg* 1987; **66**: 401–6

Rawal N, Sjostrand U, Dahlstrom B. Postoperative pain relief by epidural morphine. *Anesth Analg* 1981; **60**: 726–31

Rawal N, Sjostrand U, Christoffersson E, Dahlstrom B, Arvill A, Rydman H. Comparison of intramuscular and epidural morphine for postoperative analgesia in the grossly obese *Anesth Analg* 1984, **63**· 583–92

Rawal N, Schott U, Dahlstrom B, *et al* Influence of naloxone infusion of analgesia and respiratory depression following epidural morphine. *Anesthesiology* 1986; **64**: 194–201

Renaud B, Brichant JF, Clergue F, Chauvin M, Levron JC, Viars P. Ventilatory effects of continuous epidural infusion of fentanyl. *Anesth Analg* 1988; **67**: 971–5

Rosenberg PH, Heino A, Scheinin B. Comparison of intramuscular analgesia, intercostal block, epidural morphine and on-demand intravenous fentanyl in the control of pain after upper abdominal surgery. *Acta Anaesthesiol Scand* 1984; **28**: 603–7

Ross R, Clarke J, Armitage E. Postoperative pain prevention by continuous epidural infusion. *Anaesthesia* 1980; **35**: 663–8

Rosseel PM, van den Broek WG, Boer EC, Prakash O. Epidural sufentanil for intra and postoperative analgesia in thoracic surgery: a comparative study with intravenous sufentanil. *Acta Anaesthesiol Scand* 1988; **32**: 193–8

Rygnestad T, Borchgrevink P, Eide E Postoperative epidural infusion of morphine and bupivacaine is safe on surgical wards. *Acta Anaesthesiol Scand* 1997; **41**: 868–79

Rygnestad T, Zahlsen K, Bergslien O, *et al.* Focus on mobilisation after lower abdominal surgery. A double blind randomised comparison of epidural bupivacaine with morphine versus lidocaine with morphine postoperative analgesia *Acta Anaesthesiol Scand* 1999, **43**: 380–7

Salomaki TE, Laitinen JO, Nuutinen LS. A randomized double blind comparison of epidural versus intravenous fentanyl infusion for analgesia after thoracotomy. *Anesthesiology* 1991; **75**: 790–5

Salomaki TE, Laitinen JO, Vainionpaa V, Nuutinen LS. 0 1% bupivacaine does not reduce the requirement for epidural fentanyl infusion after major abdominal surgery *Reg Anesth* 1995, **20**. 435–43

Salomaki T, Kokki H, Turunen M. Havukainen U, Nuutinen L Introducing epidural fentanyl for on-ward pain relief after major surgery *Acta Anaesthesiol Scand* 1996; **40**. 704–9

Sandler AN, Stringer D, Panos L, *et al.* A randomized double-blind comparison of lumbar epidural and iv fentanyl infusions for post-thoracotomy pain relief *Anesthesiology* 1992; **77** 626–34

Sands RP, de Leon-Casasola OA, Harrison P, Velagapudi S, Lema MJ. Randomised double blind comparison of epidural and intravenous fentanyl for postoperative pain. *Acute Pain* 1997; **1**: 7–14

Sawchuck CW, Ong B, Unruh HW, Horan TA, Greengrass R. Thoracic versus lumbar epidural fentanyl for post-thoracotomy pain. *Ann Thorac Surg* 1993; **55**: 1472–6

Schug SA, Fry RA. Continuous regional analgesia in comparison with intravenous opioid administration for routine postoperative pain control. *Anaesthesia* 1994, **49**: 528–32

Schultz A-M, Werba A, Ulbing S, Gollmann G, Lehofer F Perioperative thoracic epidural analgesia for thoracotomy. *Eur J Anaesthesiol* 1997; **14**: 600–3

Scheinin B, Asantila R, Orko R. The effect of bupivacaine and morphine on pain and bowel function after colonic surgery *Acta Anaesthesiol Scand* 1987; **31**: 161–4

Schwartz BR, Gregg RV, Kessler DL, Bracken RB. Continuous postoperative epidural analgesia in management of postoperative surgical pain. *Urology* 1989; **34**. 349–52

Scott DA, Beilby DS, McClymont C. Postoperative analgesia using epidural infusions of fentanyl with bupivacaine *Anesthesiology* 1995, **82**: 727–37

Scott DA, Chamley DM, Mooney PH, Deam R, Mark AH, Hagglof B. Epidural ropivacaine infusion for postoperative analgesia after major lower abdominal surgery—a dose finding study *Anesth Analg* 1995; **81**· 982–6

Scott NB, James K, Murphy M, Kehlet H. Continuous thoracic epidural analgesia versus combined spinal/thoracic epidural analgesia on pain, pulmonary function and metabolic response following colonic surgery. *Acta Anaesthesiol Scand* 1996; **40**· 691–6

Shir Y, Raja SN, Frank SM. The effect of epidural versus general anesthesia on postoperative pain and analgesic requirements in patients undergoing radical prostatectomy. *Anesthesiology* 1994; **80**: 49–56

Sidebotham DA, Russell K, Dijkhuizen M, Tester P, Schug SA. Low dose fentanyl improves continuous bupivacaine epidural analgesia following orthopaedic, urological or general surgery *Acute Pain* 1997; **1**: 27–32

Singh H, Bossard R, White P, Yeatts R. Effects of ketorolac v bupivacaine coadministration during patient controlled hydromorphone epidural analgesia after thoracotomy procedures. *Anesth Analg* 1997; **84**· 564–9

Sjostrom S, Hartvig D, Tamsen A Patient controlled analgesia with extradural morphine or pethidine. *Br J Anaesth* 1988, **60**· 358–66

Snijdelaar DG, Hasenbos MA, van Egmond J, Wolff AP, Liem TH High thoracic epidural sufentanil with bupivacaine. continuous infusion of high volume versus low volume *Anesth Analg* 1994, **78**· 490–4

Stenseth R, Sellevold O, Breivik H Epidural morphine for postoperative pain: experience with 1085 patients *Acta Anaesthesiol Scand* 1985, **29**· 148–56

Stuart-Taylor ME, Billingham IS, Barrett RF, Church JJ. Extradural diamorphine for postoperative analgesia: audit of a nurse-administered service to 800 patients in a district general hospital. *Br J Anaesth* 1992; **68**: 429–32

Torda TA, Pybus DA Clinical experience with epidural morphine *Anaesth Intensive Care* 1981; **9**: 129–34

Tsui SL, Chan CS, Chan AS, Wong SJ, Lam CS, Jones RD Postoperative analgesia for oesophageal surgery: a comparison of three analgesic regimens. *Anaesth Intensive Care* 1991, **19**· 329–37

Tsui SL, Lo RJ, Tong W, *et al.* A clinical audit for postoperative pain control on 1443 surgical patients *Acta Anaesthesiol Sin* 1995; **33**: 137–48

Tsui SL, Lee DK, Ng KF, Chan TY, Chan WS, Lo JW. Epidural infusion of bupivacaine plus fentanyl provides better postoperative analgesia than patient controlled analgesia with intravenous morphine after gynaecological laparotomy. *Anaesth Intensive Care* 1997, **25**: 476–81

Vandermeersch E. Epidural PCA with bupivacaine and sufentanil. *Acta Anaesthesiol Belgica* 1992; **43**: 71–4

Wheatley RG, Madej TH, Jackson IJ, Hunter D. The first year's experience of an Acute Pain service. *Br J Anaesth* 1991; **67**: 353–9

White WD, Pearce DJ, Norman J. Postoperative analgesia: a comparison of intravenous on-demand fentanyl with epidural bupivacaine. *BMJ* 1979; **2**: 166–7

Wong LT, Koh LH, Kaur K, Boey SK. A two-year experience of an Acute Pain service in Singapore. *Singapore Med J* 1997; **38**: 209–13

Writer WD, Hurtig JB, Evans D, Needs RE, Hope CE, Forrest JB. Epidural morphine prophylaxis of postoperative pain: report of a double blind multicentre study. *Can Anaesth Soc J* 1985; **32**: 330–8

Appendix V

References used to calculate incidence of premature catheter dislodgement

Badner NH, Reimer EJ, Komar WE, Moote CA. Low dose bupivaciane does not improve postoperative epidural fentanyl analgesia in orthopaedic patients. *Anesth Analg* 1991; **72**: 337–41

Badner NH, Komar WE. Bupivacaine 0.1% does not improve postoperative epidural fentanyl analgesia after abdominal or thoracic surgery. *Can J Anaesth* 1992; **39**: 330–6

Baron CM, Kowalski SE, Greengrass R, Horan TA, Unruh HW, Baron CL. Epinephrine decreases postoperative requirements for continuous thoracic epidural fentanyl infusions. *Anesth Analg* 1996; **82**: 760–5

Bredtmann RD, Herden HN, Teichmann W, *et al.* Epidural analgesia in colonic surgery: results of a randomised prospective study. *Br J Surg* 1990; **77**: 638–42

Brodsky JB, Chaplan SR, Brose WG, Mark JB. Continuous epidural hydromorphone for postthoracotomy pain relief. *Ann Thorac Surg* 1990; **50**: 888–93

Broekema AA, Gielen MJ, Hennis PJ. Postoperative analgesia with continuous epidural sufentanil and bupivacaine. *Anesth Analg* 1996; **82**: 754–9

Burstal R, Wegener F, Hayes C, Lantry G. Epidural analgesia: prospective audit of 1062 patients. *Anaesth Intensive Care* 1998; **26**: 165–72

Dahl JB, Hansen BL, Hjortso NC, Erichsen CJ, Molniche S, Kehlet H. Influence of timing on the effect of continuous extradural analgesia with bupivacaine and morphine after major abdominal surgery. *Br J Anaesth* 1992; **69**: 4–8

Etches RC, Gammer T-L, Cornish R. Patient controlled epidural analgesia after thoracotomy: a comparison of meperidine with and wihout bupivacaine. *Anesth Analg* 1996; **83**: 81–6

Grant G, Boyd A, Zakowski M, *et al.* Thoracic versus lumbar administration of epidural morphine for postoperative analgesia after thoracotomy. *Reg Anesth* 1993; **18**: 351–5

Griffiths DP, Diamond AW, Cameron JD. Postoperative extradural analgesia following thoracic surgery: a feasibility study. *Br J Anaesth* 1975; **47**: 48–54

Ilahi OA, Davidson JP, Tullos HS. Continuous epidural analgesia using fentanyl and bupivacaine after total knee arthroplasty. *Clin Orthop Related Res* 1994; **299**: 44–52

Jayr C, Beaussier M, Gustafsson Y, *et al.* Continuous epidual infusion of ropivacaine for postoperative analgesia after abdominal surgery. *Br J Anaesth* 1998; **81**: 887–92

Johnson RG, Miller M, Murphy M. Intraspinal narcotic analgesia: a comparison of two methods of postoperative pain relief. *Spine* 1989; **14**: 363–6

Lee A, Simpson D, Whifield A, Scott DB. Postoperative analgesia by continuous extradural infusion of bupivacaine and diamorphine. *Br J Anaesth* 1988; **60**: 845–50

de Leon-Casasola OA, Parker B, Lema M, Harrison P, Massey J. Postoperative epidural bupivacaine–morphine therapy. *Anesthesiology* 1994; **81**: 368–75

Liu SS, Allen HW, Olsson GL. Patient controlled epidural analgesia with bupivacaine and fentanyl on hospital wards. *Anesthesiology* 1998; **88**: 688–95

Lubenow TR, Faber LP, McCarthy RJ, Hopkins EM, Warren WH, Ivankovitch AD. Post-thoracotomy pain management using continuous epidural analgesia in 1324 patients. *Ann Thorac Surg* 1994; **58**: 924–30

Mahoney OM, Noble PC, Davidson J, Tillos HS. The effect of continuous epidural analgesia on postoperative pain, rehabilitation and duration of hospitalisation in total knee arthroplasty. *Clin Orthop Related Res* 1990, **260**: 30–7

Mehnert JH, Dupont TJ, Rose DH. Intermittent epidural morphine instillation for control of postoperative pain. *Am J Surg* 1983; **146**: 145–51

Melendez JA, Cirella VN, Delphin ES. Lumbar epidural fentanyl analgesia after thoracic surgery. *J Cardiothor Anesth* 1989; **3**: 150–3

Paech MJ, Pavy TJ, Evans SF. Single-dose prophylaxis for postoperative nausea and vomiting after major abdominal surgery: ondanseteron versus droperidol. *Anaesth Intensive Care* 1995; **23**: 548–54

Paech MJ, Pavy TJ, Orlikowski CE, Lim W, Evans SF. Postoperative epidural infusion: a randomised double blind dose finding trial of clonidine in combination with bupivacaine and fentanyl. *Anesth Analg* 1997; **84**: 1323–8

Rapp SE, Ready LB, Greer BE. Postoperative pain management in gynecologic oncology patients utilizing epidural opiate analgesia and PCA. *Gynecol Oncol* 1989; **35**: 341–4

Ready LB, Loper KA, Nessly M, Wild L. Postoperative epidural morphine is safe on surgical wards. *Anesthesiology* 1991; **75**: 452–6

Salomaki TE, Kokki H, Turunen M, Havukainen U, Nuutinen LS. Introducing epidural fentanyl for on-ward pain relief after major surgery. *Acta Anaesthesiol Scand* 1996; **40**: 704–9

Sawchuck CW, Ong B, Unruh HW, Horan TA, Greengrass R. Thoracic versus lumbar epidural fentanyl for post-thoracotomy pain. *Ann Thorac Surg* 1993; **55**: 1472–6

Schug SA, Fry RA. Continuous regional analgesia in comparison with intravenous opioid administration for routine postoperative pain control. *Anaesthesia* 1994; **49**: 528–34

Scott DA, Beilby DS, McClymont C. Postoperative analgesia using epidural infusions of fentanyl with bupivacaine. *Anesthesiology* 1995; **82**: 727–37

Tsui SL, Lee DK, Ng KF, Chan TY, Chan WS, Lo JW. Epidural infusion of bupivacaine plus fentanyl provides better postoperative analgesia than patient controlled analgesia with intravenous morphine after gynaecological laparotomy. *Anaesth Intensive Care* 1997; **25**: 476–81

Welch DB, Hrynaszkiewicz A. Post-operative analgesia using epidural methadone: administration by the lumbar route for thoracic pain relief. *Anaesthesia* 1981; **36**: 1051–4

Wong LT, Koh LH, Kaur K, Boey SK. A two-year experience of an Acute Pain service in Singapore. *Singapore Med J* 1997, **38**: 209–13

References

1 Ready B, Oden R Chadwick H, *et al.* Development of an anesthesiology-based postoperative pain management service. *Anesthesiology* 1988; **68**: 100–6

2 Maier C, Kibbel K, Mercker S, Wulf H. Postoperative pain therapy at general nursing stations. An analysis of eight years experience at an anaesthesiological acute pain service. *Anaesthesist* 1994; **43**: 385–97

3 Commission on the Provision of Surgical Services. *Pain After Surgery.* Royal Colleges of Surgeons and Anaesthesists, London, 1990

4 Agency for Health Care Policy and Research. *Clinical Practice Guideline. Acute Pain Management. Operative or Medical Procedures of Trauma.* AHCPR, Rockville, 1992

5 Ready LB, Ashburn M, Caplan RA, *et al.* Practice guidelines for acute pain management in the peri-operative setting· a report of the American Society of Anesthesiologists task force on pain managenment *Anesthesiology* 1995; **82**: 1071–81

6 Clinical Standards Advisory Group. *Services for Patients with Pain.* Department of Health, London, 1999

7 American Society of Anesthesiologists *Practice Guidelines for the Management of Acute Pain in the Perioperative Setting.* ASA, 1995

8 Audit Commission. *Anaesthesia Under Examination* Audit Commission, London, 1997

9 Rawal N, Allvin R. Epidural and intrathecal opioids for postoperative pain management in Europe: a 17 nation questionnaire study of selected hospitals. *Acta Anaesthesiol Scand* 1996; **40**: 1119–26

10 Armitage P, Berry G. *Statistical Methods in Medical Research*, 3rd Edn. Oxford: Blackwell, 1994

11 Marquardt HM, Razis PA. Prepacked take-home analgesia for day case surgery. *Br J Nursing* 1994; **5**: 114–8

12 Loan WB, Dundee JW. The value of the study of postoperative pain in the assessemnt of analgesics. *Br J Anaesth* 1967; **39**: 745–50

13 Thompson SG Why sources of heterogeneity in meta-analysis should be investigated. *BMJ* 1994; **309**: 1351–5

14 Moriarty A, Mollenbrock G, Johnstone B, Potter GE. A ward-based, nurse managed, acute pain service in a district general hospital. *Today's Anaesthetist* 1993, **8**. 92–4

15 Liu W, Aitkenhead A. Comparison of contemporaneous and retrospective assessment of postoperative pain using the visual analogue scale. *Br J Anaesth* 1991; **67**: 768–71

16 Collins SL, Moore RA, McQuay HJ. The visual analogue pain intensity scale: what is moderate pain in millimetres? *Pain* 1997; **72**: 95–7

17 Schug SA, Fry RA. Continuous regional analgesia in comparison with intravenous opioid administration for routine postoperative pain control. *Anaesthesia* 1994; **49**: 528–32

18 Sidebotham DA, Russell K, Dijkhuizen MR, Tester P, Schug SA Low dose fentanyl improves continuous bupivacaine epidural analgesia following orthopaedic, urological or general surgery *Acute Pain* 1997; **1**: 27–32

19 Rygnestad T, Zahlsen K, Bergslien O, *et al.* Focus on mobilisation after lower abdominal surgery. A double blind randomised comparison of epidural bupivacaine with morphine versus lidocaine with morphine for postoperative analgesia. *Acta Anaesthesiol Scand* 1999; **43**· 380–387

20 de Leon-Casasola OA, Parker B, Lema MJ, Harrison P, Massey J. Postoperative epidural bupivacaine-morphine. Experience with 4,227 surgical cancer patients. *Anesthesiology* 1994; **81**. 308–15

21 Benhamou D. Measurement of postoperative pain. *Ann Fr Anaesth Reanimation* 1998; **17**: 555–71

22 Rawal N, Sjostrand U, Christoffersson E, Dahlstrom B, Arvill A, Rydman H. Comparison of intramuscular and epidural morphine for postoperative analgesia in the grossly obese. *Anesth Analg* 1984; **63**: 583–92

23 Gould TH, Crosby DL, Harmer M, *et al.* Policy for controlling pain after surgery: effect of sequential changes in management. *BMJ* 1992; **305**: 1187–93

24 Scott DA, Chamley DM, Mooney PH, Deam RK, Mark AH, Hagglof B. Epidural ropivacaine infusion for postoperative analgesia after major lower abdominal surgery—a dose finding study. *Anesth Analg* 1995; **81**: 982–98

25 Stenseth R, Sellevold O, Breivik H. Epidural morphine for postoperative pain: experience with 1085 patients. *Acta Anaesthesiol Scand* 1985; **29**: 148–56

26 Wheatley RG, Madej TH, Jackson IJ, Hunter D. The first year's experience of an Acute *Pain* service. *Br J Anaesth* 1991; **67**: 353–9

27 DonovanB. Patient attitudes to postoperative pain relief. *Anaesth Intensive Care* 1983; **11**: 125–8

28 Ferrante F, Ostheimer G, Covino B, eds. *Patient Controlled Analgesia.* Oxford· Blackwell Scientific, 1990

British Journal of Anaesthesia 89 (3): 424–7 (2002)

Comparison of morphine alone with morphine plus clonidine for postoperative patient-controlled analgesia

S. A. Jeffs[1*], J. E. Hall[1] and S. Morris[2]

[1]University of Wales College of Medicine, Heath Park, Cardiff CF14 4XN, UK. [2]Department of Anaesthetics and Intensive Care Medicine, Llandough Hospital, Penlan Road, Llandough, Penarth, South Glamorgan, UK

**Corresponding author*

Background. Clonidine is an α_2 adrenergic agonist with analgesic properties. This study aimed to see if the addition of clonidine to morphine when given by patient-controlled analgesia (PCA) would improve analgesia beyond the first 12 h after surgery.

Methods. Sixty patients undergoing lower abdominal surgery were recruited into a randomized double blind study. At the end of surgery Group C received an infusion of clonidine 4 μg kg^{-1} over 20 min, PCA clonidine 20 μg and morphine 1 mg bolus. Group M received an infusion of saline and then PCA morphine 1 mg bolus. Pain, sedation and nausea and vomiting were assessed after 12, 24 and 36 h, and satisfaction with analgesia was assessed at 36 h.

Results. Pain scores were significantly lower in Group C between 0 and 12 h, but thereafter there was no difference. Morphine consumption was the same for both groups until 24–36 h. Nausea and vomiting was significantly reduced in Group C between 0 and 24 h. Patients in Group C were significantly happier with their pain relief (four-point scale).

Br J Anaesth 2002; **89**: 424–7

Keywords: agonists, adrenergic; analgesia, patient-controlled; analgesics opioid, morphine; pharmacology, clonidine; pharmacology, morphine; vomiting, nausea, anaesthetic factors

Accepted for publication: April 26, 2002

The morphine sparing effects of the α_2-adrenoreceptor agonist, clonidine, have been well demonstrated at initial bolus doses of between 2 and 8 μg kg^{-1}.[1–7] Clonidine has been used successfully for supplementing analgesia intraoperatively,[1] postoperatively[2] and in intensive care,[3] although most studies have looked either at its immediate effect or its effect during the first 12 h after surgery. Clonidine has largely been delivered either orally (as a premedication), or as an i.v. infusion.[1–6] One study compared clonidine epidurally with patient-controlled analgesia (PCA) but as the sole analgesic medication.[7] Oral and i.v. modes of delivery have potential problems for postoperative pain relief. The absorption of oral analgesic drugs is unpredictable in the perioperative period, especially after major surgery. In addition, it may not be desirable to give a bolus of a vasoactive drug in the immediate postoperative period. Intravenous infusions overcome the problem of bolus doses by being titratable (although this is more difficult with clonidine because of its long elimination half-life[8]), but this type of delivery needs greater nursing supervision, which may not be readily available on ordinary wards.

PCA has been used extensively over recent years to titrate analgesia to need[9] thus avoiding the potential problems of overdose. PCA is widely used in ordinary ward situations. This randomized double blind study was designed to see if the addition of clonidine to morphine in a PCA device would reduce postoperative morphine consumption when compared with morphine alone. The study followed patients for 36 h after surgery to see how long any effect could be maintained. Any associated reduction in nausea and vomiting was assessed. Although reduced nausea and vomiting have been demonstrated with clonidine usage before,[5 10 11] this study examined a very high-risk population i.e. females undergoing lower abdominal surgery.

Methods

With local research ethics committee approval, 60 patients between the ages of 18 and 75 yr were recruited to a randomized double blind study. All patients were ASA grade I or II, undergoing major lower abdominal or gynaecological surgery. Patients were excluded if there was a history of hypertension, ischaemic heart disease or

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

conduction disturbance, a history of depression or alcohol abuse, if they were taking antidepressants or β-adrenoreceptor blockers, if they had impaired hepatic or renal function or a known sensitivity to opioids or clonidine.

Patients were given oral and written information about the study, and written consent was obtained. They were instructed in the use of the PCA device at the preoperative visit. An Abbott Provider 5500™ device was used to deliver the study drugs.

All patients were premedicated with temazepam 20 mg 1.5 h before surgery and a standard anaesthetic was given. After pre-oxygenation, anaesthesia was induced with propofol 2 mg kg^{-1}, droperidol 1 mg, fentanyl 1 μg kg^{-1} and vecuronium 0.1 mg kg^{-1}. Anaesthesia was maintained by 1–2% isoflurane in nitrous oxide and oxygen (ratio 2:1). Further boluses of fentanyl 1 μg kg^{-1} were given intraoperatively, up to a maximum of 4 μg kg^{-1}, at the anaesthetist's discretion depending on the type and duration of surgery. The total amount of fentanyl administered to each patient was recorded.

Intraoperatively, patients were randomized into two groups: Group C received clonidine 4 μg kg^{-1} in 100 ml of normal saline and Group M received 100 ml of normal saline. Both were given over 20 min when the surgeon started to close the abdomen at the end of the procedure. After surgery, patients in Group C received a bolus of morphine 1 mg and clonidine 20 μg with a 5 min lockout time and patients in Group M received a 1 mg morphine bolus, also with a 5 min lockout time. The PCA dose of clonidine was based on a 2 μg kg^{-1} h^{-1} infusion[12] divided by seven (an audit was undertaken prior to commencing the study to assess the average number of PCA doses this group of patients needed in 1 h). Clonidine and morphine are physically and chemically compatible.[13] Patients were studied for 36 h after surgery

As soon as the patients were awake in the recovery room, their pain was assessed using a four-point verbal rating score (0, no pain; 1, mild pain; 2, moderate pain; 3, severe pain). If the pain score was 2 or above, a recovery nurse, who was unaware of the randomization, titrated morphine 2 mg at 5-min intervals until the pain score was below 2. The PCA device, containing the appropriate study drug, was then connected to the i.v. infusion. Patients were assessed at 12, 24 and 36 h after surgery and asked to score their worst pain since the previous assessment. These scores were all on movement in the bed. Morphine consumption at these times was recorded.

After surgery, sedation was assessed on a four-point scale (0, awake and alert; 1, drowsy; 2, mostly sleeping; 3, difficult or impossible to awaken). Sedation scores were recorded 12, 24 and 36 h after surgery.

The presence of nausea and vomiting was noted using a four-point scale (0, no nausea or vomiting; 1, mild nausea; 2, severe nausea; 3, retching or vomiting), with all incidents being noted on the data collection sheet as they occurred. Patients with a nausea score of 2 or 3 were given cyclizine 50 mg intravenously and odansetron 4 mg if this was unsuccessful. The number of patients who vomited and the severity of any episode in each 12 h time period were recorded. After 36 h patients were asked to score their level of satisfaction with their postoperative pain relief up to that time on a four-point scale (1, totally dissatisfied; 2, moderately dissatisfied; 3, reasonably satisfied; 4, totally satisfied with pain relief).

The power calculation for the study was based on morphine consumption between 12 and 24 h after surgery. A retrospective survey of morphine consumption in patients undergoing hysterectomy revealed a mean of 30 (SD 12) mg morphine between 12 and 24 h after surgery. Using Altman's Nomogram this gives a standardized difference of 0.83. To demonstrate a 30% decrease in morphine consumption between 12 and 24 h after surgery, 60 patients would be needed for a study with a power of 0.8 to show a significant difference at the $P<0.05$ level.

The patients were randomized by computer. Blinding was carried out by a doctor, not involved in the data collection, who made up syringes containing morphine with or without clonidine such that they appeared identical. Morphine consumption was analysed using Student's unpaired *t*-test. The Mann–Whitney *U* test was used for pain, sedation and nausea and vomiting scores and χ^2 analysis was used for the number of patients who experienced nausea or vomiting A probability level of <0.05 was considered to be statistically significant.

Results

There were no differences with respect to patient characteristics of the two groups (Table 1) Many more females than males were recruited as many were undergoing total

Table 1 Patient characteristics and intraoperative fentanyl consumption (mean (SD or range) or ratio)

	Morphine and clonidine combined (*n*=30)	Morphine alone (*n*=30)
Age (yr)	42 (29–74)	47 (23–68)
Sex (f:m)	25 5	25 5
Weight (kg)	68 (12)	69 (10)
Intraoperative fentanyl usage (μg)	179 (66)	191 (60)

Table 2 Pain scores (median (range)) and morphine consumption and (mean (SD)) in each 12-h period $^*P<0\ 05$

Time after surgery (h)	Postoperative pain score		Morphine consumption (mg)	
	Group C	Group M	Group C	Group M
12	1* (0–3)	3 (1–4)	32 (13)	36 (15)
24	0 (0–2)	0 (0–2)	25 (12)	28 (14)
36	0 (0–1)	0 (0–1)	15* (8)	21 (12)

Table 3 Incidence and severity of nausea and vomiting, and sedation scores (median (range)) in each 12-h period. $^*P<0.05$

Time after surgery (h)	Nausea and vomiting (*n*)		Severity of nausea and vomiting		Sedation scores	
	Group C	Group M	Group C	Group M	Group C	Group M
12	4*	11	0 (0–1)	0 (0–3)	2 (0–2)	2 (1–3)
24	3*	11	0 (0–1)	0 (0–2)	1 (0–2)	1 (0–2)
36	1	4	0 (0–1)	0 (0–2)	0 (0–2)	1 (0–2)

abdominal hysterectomy. In the clonidine and morphine only groups, there were 23 patients having a gynaecological procedure, two female patients and five male patients undergoing a general surgical procedure. There was no difference in the dose of intraoperative fentanyl used between the two groups (Table 1). All patients were monitored fully throughout the study. No patients were withdrawn due to cardiovascular instability, and nor did any patient require intervention as a result of cardiovascular problems.

Pain scores were measured on movement in the bed and the worst score in the time period recorded. These were significantly lower in the first 12 h in Group C (Table 2), but thereafter there were no differences. The doses of morphine used by the two groups can be seen in Table 2. For the first 24 h, morphine consumption in the clonidine group was only marginally reduced and the reduction in consumption only achieved statistical significance during the final 12 h of the study. The incidence of postoperative nausea and vomiting was significantly reduced in Group C during the first 24 h (Table 3), although the severity scores were unchanged. There were no differences in the sedation scores between the two groups (Table 3). Patients' satisfaction scores were significantly higher in Group C (median 4 (range 2–4), compared with 3 (1–4) in Group M; $P<0.05$).

Discussion

In this study, the perioperative use of clonidine in addition to morphine produced improved analgesia during the first 12 h after major surgery. However, there was no improvement after this time. There was no significant reduction in the amount of morphine consumed. The combination of morphine and clonidine were associated with a reduction in postoperative nausea and vomiting, the effects of which were seen for 24 h after surgery. Presumably the combination of improved early pain relief and reduced nausea and vomiting in Group C led to the increased patient satisfaction in this group.

The improved analgesia was not sustained past the first 12 h after surgery in this study. This may well have been because plasma clonidine concentrations were not sustained by the parameters set for the PCA device. Indeed, the enhanced analgesic effect may have been achieved by the clonidine loading dose alone. Future studies examining the use of clonidine analgesia after the first 12 h after surgery would probably benefit from measuring plasma clonidine concentrations.

The use of perioperative clonidine in this study significantly decreased nausea and vomiting in a group of patients at high risk of experiencing this problem. Nausea and vomiting is a major problem after surgery, affecting up to 75% of patients, depending on their age and the type of procedure carried out.[14] The reduction in nausea and vomiting associated with clonidine has been reported previously.[5 10 11] Clonidine has also been used to treat nausea and vomiting in a diabetic patient who had not responded to conventional treatment.[15] In addition, it is known that patients undergoing chemotherapy experience anticipatory nausea and vomiting. This is thought to be due to noradrenergic activity. There have been pilot studies to look at this and, although differences were seen, further studies were thought to be needed.[16] Anticipatory nausea and vomiting may also be a problem perioperatively, as many patients worry about feeling sick after their operation, especially if they have had the problem before. Again, it has been suggested that noradrenergic activity may be responsible for these symptoms. Plasma 3-methyl-4-hydroxyphenlglycol, a metabolite of norepinephrine, is elevated during anxiety. Clonidine, acting at presynaptic α_2 adrenoreceptors, reduces noradrenergic activity[17] and this may account for its effects on nausea and vomiting. Clonidine also has sedative effects. These are thought to be mediated by α_2 adrenoreceptors in the locus coeruleus[17] and it may be a combination of decreased norepinephrine activity and sedation that causes the antiemetic effect, particularly as midazolam and subhypnotic doses of propofol have a similar effect.[18] The use of clonidine in a PCA may represent a strategy for dealing with a patient who states a history of previous severe nausea (with or without vomiting) that was resistant to treatment.

References

1 De Kock MF, Pinchon G, Scholtes J-L. Intraoperative clonidine enhances postoperative morphine patient-controlled analgesia. *Can J Anaesth* 1992; **39**: 537–44

2 Bernard J-M, Hommeril J-L, Passuti N, Pinaud M. Postoperative analgesia by intravenous clonidine. *Anesthesiology* 1991; **75**: 577–82

3 Lyons B, Casey W, Doherty P, McHugh M, Moore KP. Pain relief with low-dose intravenous clonidine in a child with severe burns. *Intensive Care Med* 1996; **22**: 249–51

4 Benhamou D, Narchi P, Hamza J, Marx M, Peyrol M-T, Sembeil F.

Addition of oral clonidine to postoperative patient-controlled analgesia with i.v. morphine. *Br J Anaesth* 1994; **72**: 537–40

5 Park J, Forrest J, Kolesar R, Bhola D, Beattie S, Chu C. Oral clonidine reduces postoperative PCA morphine requirements. *Can J Anaesth* 1996; **43**: 900–6

6 Flacke JW, Bloor BC, Flacke WE, *et al.* Reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary bypass surgery. *Anesthesiology* 1987; **67**: 11–9

7 Bernard J-M, Kick O, Bonnet F. Comparison of intravenous and epidural clonidine for postoperative patient-controlled analgesia *Anesth Analg* 1995; **81**: 706–12

8 Davies DS, Wing LMH, Reid JL, *et al.* Pharmacokinetics and concentration-effect relationships of intravenous and oral clonidine. *Clin Pharmacol Ther* 1977; **21**: 593–601

9 Lehman KA. Patient controlled analgesia: An efficient therapeutic tool in the postoperative setting. *Eur Surg Res* 1999, **31**: 112–21

10 Mikawa K, Nishina K, Maekawa N, Asano M, Obara H. Oral clonidine premedication reduces vomiting in children after strabismus surgery. *Can J Anaesth* 1995; **42**: 977–81

11 Kobayashi N, Ishii S. Effectiveness of clonidine in postoperative nausea and vomiting – epidural *versus* oral administration *Masui* 1997; **46**: 538–42

12 Ryszard J, Zochawski, Wojciech Lada. Intravenous clonidine treatment in acute myocardial infarction (comparison to a nitroglycerin-treated and control group). *J Cardiovasc Pharmacol* 1986; **8** (suppl 3): S41–5

13 Christi JM, Jones CW, Markowsky SJ Chemical compatibility of regional anesthetic drug combinations. *Ann Pharmacother* 1992; **26**: 1078–80

14 Lerman J. Surgical and patient factors involved in postoperative nausea and vomiting. *Br J Anaesth* 1992; **69**: 24S–32S

15 Soergel KH, Greenburger NJ. Nausea and vomiting in the diabetic patient. *Hosp Pract* 1998; **33**. 43–62

16 Fetting JH, Sheidler VR, Stefanek ME, Enterline JP. Clonidine for anticipatory nausea and vomiting: a pilot study. *Cancer treat rep* 1987; **71**: 409–10

17 Bloor BC. General pharmacology of α_2-adrenoreceptors *Anaesth Pharmacol Rev* 1993; **1**: 221–32

18 Hvarfner A, Hammas B, Thorn SE, Wattwil M. The influence of propofol on vomiting induced by apomorphine *Anesth Analg* 1995; **80**: 967–9

British Journal of Anaesthesia **89** (3): 428–37 (2002)

Contribution of midazolam and its 1-hydroxy metabolite to preoperative sedation in children: a pharmacokinetic-pharmacodynamic analysis

T. N. Johnson[1]*, A. Rostami-Hodjegan[1], J. M. Goddard[2], M. S. Tanner[3] and G. T. Tucker[1]

[1]*University of Sheffield, Academic Unit of Molecular Pharmacology and Pharmacogenetics, Division of Clinical Sciences (South), The Royal Hallamshire Hospital, Sheffield S10 2JF, UK.* [2]*Department of Anaesthesia, Children's Hospital, Sheffield S10 2TH, UK.* [3]*University of Sheffield, Academic Unit of Child Health, Children's Hospital, Sheffield S10 2TH, UK*

**Corresponding author*

Background. Oral midazolam is widely used for preoperative sedation in children. We have studied the pharmacokinetics (PK) of both midazolam and its active 1-hydroxy metabolite and their contributions to sedative effect in 45 children attending for day surgery.

Methods. Blood samples (two per individual) were collected at the beginning and end of the surgical procedure. Plasma midazolam and 1-hydroxymidazolam (1-OHMDZ) were measured by HPLC. Sedation score (score: 1=awake, 2=drowsy/asleep) was recorded at the same time as the first blood sample. The population-PK software P-Pharm was used to analyse the data. Age, weight, sex, concomitant drugs, and the metabolic ratio, 1-OHMDZ/midazolam were investigated as co-variates of the PK of midazolam and 1-OHMDZ. The pharmacokinetic-pharmacodynamic (PK-PD) modelling of the score in relation to plasma midazolam and 1-OHMDZ was performed using logistic regression analysis.

Results. A median dose of 0.5 mg kg^{-1} was given to the children, median age 5 yr (range from 9 months to 12 yr) and weight 21 kg (range 8–75 kg). Average concentrations of midazolam 150 ng ml^{-1} and 1-OHMDZ 90 ng ml^{-1} were observed in the first plasma samples. These concentrations resulted in an odds ratio of 4 in favour of score 2 *vs* 1. The best PK-PD model included both midazolam and 1-OHMDZ as active moieties and predicted correct scores in 86% of cases.

Conclusion. Studies of midazolam should evaluate the contribution of 1-OHMDZ to the overall PD effect. The metabolite 1-OHMDZ has approximately half the activity of the parent drug and can compensate for at least part of the decreased effect due to increased midazolam metabolism.

Br J Anaesth 2002; **87**: 428–37

Keywords: hypnotics benzodiazepine, midazolam; pharmacokinetics, midazolam; pharmacodynamics; sedation, preoperative; anaesthesia, paediatric

Accepted for publication: April 18, 2002

Despite the lack of a product licence for the oral route of administration and associated indications, oral midazolam is commonly used for procedural sedation in children. However, presumably because of the difficulties in obtaining multiple blood samples from a paediatric population, the PK-PD characteristics of midazolam for this indication are poorly characterized. Payne and colleagues[1] found that midazolam 0.45 mg kg^{-1} produced a sedative effect associated with plasma midazolam concentrations of 40–100 ng ml^{-1}, which is in agreement with more recent studies reporting average plasma midazolam concentrations of between 42 and 93 ng ml^{-1} after a 0.5 mg kg^{-1} dose.[2 3]

A feature of the oral administration of midazolam is a low bioavailability of around 27–36%[1 4] as a result of first-pass metabolism in both the small intestine and the liver. Thus, midazolam is hydroxylated by intestinal and hepatic cytochrome P450 3A (CYP3A) in both the 1- and 4-positions (1-OHMDZ, 4-OHMDZ). These metabolites are

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

subsequently glucuronidated and excreted in the urine. 1-OHMDZ accounts for 50–70% of the metabolism of midazolam and is reported to be pharmacologically active.[5 6] Data obtained using saccadic eye movement and electroencephalographic changes as surrogate effects after separate i.v. injections of midazolam 0.1 mg kg^{-1} and 1-OHMDZ 0.15 mg kg^{-1} suggest that 1-OHMDZ is at least as potent as the parent compound, midazolam.[6]

Studies of age-related changes in i.v. midazolam kinetics have shown a prolonged half-life and a decreased weight-corrected clearance in neonates,[7 8] an increased weight-corrected clearance to a maximum of 0.78 litre kg^{-1} h^{-1} between 1 and 2 yr of age, and then a decline to adulthood values of 0.38–0.66 litres kg^{-1} h^{-1}.[9]

We have studied the kinetics of both midazolam and 1-OHMDZ in relation to sedative effect in 45 children (from 9 months to 12 yr of age) who had received the drug orally for pre-procedural sedation. Age, weight, sex, concomitant drug therapy, and the plasma metabolic ratio (1-OHMDZ/midazolam=MR) were investigated as co-variables of PK parameters. Logistic regression analysis was used to define the PK-PD relationship between plasma midazolam and 1-OHMDZ concentrations and a simplistic but clinically relevant sedation score (score). A sparse blood sampling strategy with subsequent population-PK analysis was used to overcome the problems associated with taking multiple blood samples from children.

Methods

Patients

Forty-five children attending Sheffield Children's Hospital for day-case surgery were studied. Informed consent was obtained from each child's parent or legal guardian, and the study was approved by the South Sheffield Research Ethics Committee. Operative procedures included circumcision, inguinal hernia repair, insertion of suprapubic catheter, plastic surgery (skin tags, ear correction, extra digits), orchidopexy, in-growing toenails, and hyperspadia.

Data collection

Oral midazolam syrup (Special Products, Addlestone, UK) was administered to the patients as a pre-medication to alleviate preoperative anxiety. Age, sex, weight, biochemical renal and hepatic function tests, concurrent drug therapy, anaesthetic drugs administered, the dose of midazolam, and time of administration were recorded.

Blood samples (5 ml) were collected from an i.v. cannula into lithium-heparin tubes and labelled with the time of collection. Samples were collected at the beginning of the procedure, before any anaesthetic drugs were administered, and at the end when the i.v. cannula had been cleared with saline, thus avoiding contamination of the samples by other drugs. Using a simple rating system (1=awake, 2=drowsy/asleep), the anaesthetist recorded a sedation score (score) at the beginning of the procedure as the first blood sample was taken. The blood samples were centrifuged at 2000 *g* and 4°C for 10 min and the plasma transferred into Eppendorf tubes for storage at –80°C pending assay.

Drug and metabolite assay

The HPLC assay was based on that of Carrillo and colleagues.[10] Briefly, to 1 ml of plasma in a 15 ml screw top tube, 180 ng/50 µl of internal standard (diazepam), 1 ml of buffered glycine (0.75 M, pH 9.0) and 4 ml of methyl *tert* butyl ether were added. The samples were extracted for 30 min on a horizontal shaker and then centrifuged for 10 min at 2500 *g* The organic phase was transferred into conical glass tubes and evaporated to dryness at 37°C in a vortex evaporator (Buchler, New Jersey, USA) The residue was dissolved in 70 µl of mobile phase and 50 µl injected onto the column.

The HPLC system consisted of a Spectroflow 400 pump (Kratos Analytical Systems, New Jersey, USA), a Rheodyne valve with a 200 µl injection loop, a Waters C18 pre column, an Ultrasphere ODS, 3 µm particle size, 75×4.6 mm reverse-phase column (Beckman Instruments, California, USA), a Spectromonitor lll variable wavelength detector (Laboratory Data Control, Florida, USA) and a RE571.2 chart recorder (Venture Smith Industries, California, USA). A Hewlett Packard 931 integrator (Hewlett Packard, Waldbron, Germany) was also used alongside the chart recorder. The mobile phase was acetonitrile 40% v/v, methanol 5% v/v, and buffered acetate (pH 4.2) 55% v/v. HPLC was performed isocratically with a flow rate of 1.5 ml min^{-1} and the eluant was monitored by UV absorbance at 240 nm The retention times of parent compound and metabolites were: 4-OHMDZ (2.2 min), 1-OHMDZ (2.7 min), midazolam (3.8 min), and diazepam (4.7 min). Standard curves for the assay of 4-OHMDZ, 1-OHMDZ, and midazolam passed through the origin and were linear over the range 0–200 ng ml^{-1} with r^2 values of 0.99. The coefficient of variation at 25 ng ml^{-1} (n=6) was better than 8% for all compounds and the limit of detection was 20 nmol (approximately 7 ng ml^{-1}).

Data analysis

As only two (and in one case three) data points were collected for each subject in the present study it was not possible to use a classical analysis to obtain PK parameter values. Therefore, a population-PK approach was applied. In the population approach all data from different individuals are fitted simultaneously and *post hoc* individual kinetic parameters can be calculated with as few samples as one per individual. We used the software package P-Pharm (version 1.5, InnPhase, France). The algorithm in P-Pharm is Bayesian in nature and utilizes an expectation-maximization-like algorithm[11 12] for population parameter estimation

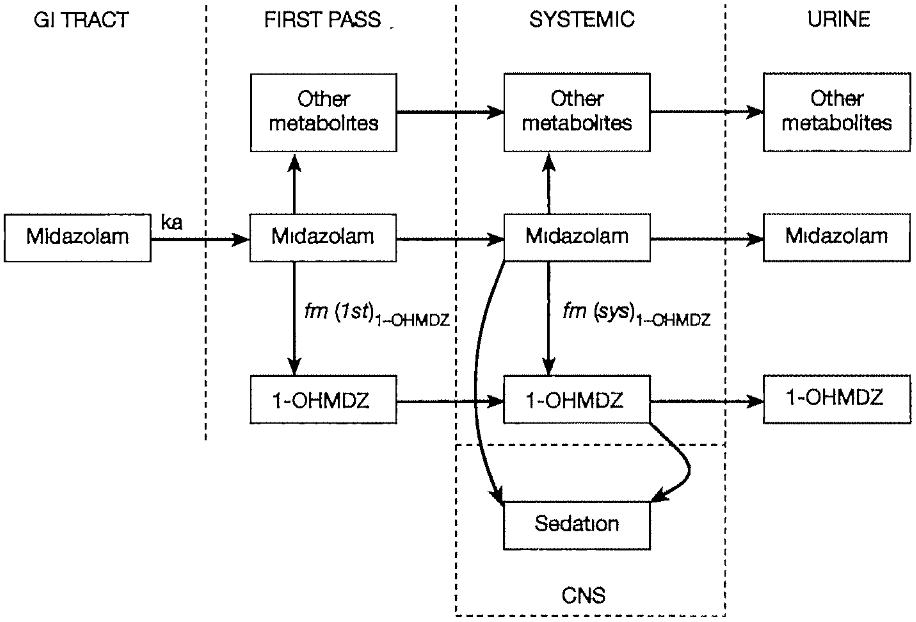


Fig 1 PK-PD model for midazolam and 1-OHMDZ.

and subsequent estimation of *post hoc* values of individual parameters.

Both one- and two-compartment models with first-order input were investigated to identify which model best described the midazolam data. The time-course of plasma midazolam was best described by a one-compartment model with first-order input. A non-uniform weighting ($1/C^2$) on measurement error together with log normal population distributions of all PK parameters were assumed following an initial inspection of different statistical models. The oral clearance (CL/F), volume of distribution (V/F), absorption rate constant (ka) and absorption lag time (t_{lag}) were considered as primary parameters; secondary parameters (such as half-life) were calculated from the primary model parameters. Initial parameter estimates for fitting procedure were obtained from the literature.[1 6 13]

Age, weight, sex, concomitant drugs (carbamazepine, propofol, thiopentone, and inhalation anaesthetics), and the metabolic ratio MR, were investigated as co-variables for each of the primary parameters. MR was determined using the following equation:

$$\mathrm{MR} = \frac{(C(t_1)_{1\text{-OHMDZ}} + C(t_2)_{1\text{-OHMDZ}}) \times \frac{1}{2}}{(C(t_1)_{\mathrm{MDZ}} + C(t_2)_{\mathrm{MDZ}}) \times \frac{1}{2}}$$

where $C(t_1)_{1\text{-OHMDZ}}$, $C(t_2)_{1\text{-OHMDZ}}$, and $C(t_1)_{\mathrm{MDZ}}$, $C(t_2)_{\mathrm{MDZ}}$ are the concentrations of 1-OHMDZ and midazolam in the first and second plasma samples, respectively. This ratio was used as a marker of combined intestinal and hepatic CYP3A activity. The PK data for 1-OHMDZ were evaluated by a two-step link model for drug and metabolite.[14] The model accounts for first-pass formation of 1-OHMDZ (fm (1st)) and subsequent systemic formation (fm (sys)). The co-variate effects were investigated for each of the primary parameters related to the PK of 1-OHMDZ, namely fm(1st), fm(sys), and k(1-OHMDZ) (the elimination rate constant for 1-OHMDZ). A representation of the PK-PD model is shown in Figure 1.

Assessment of 'best fit' among rival models was based on the Akaike Information Criteria[15] and visual inspection of the predicted *vs* measured concentration plots. The validity of the model was checked by inspection of residual distributions. The significance of co-variates was determined from stepwise multiple regression analysis (*F* values ≥5).

Considering previous reports of fast onset of action and hence rapid transfer of both midazolam and 1-OHMDZ to the CNS (transfer half lives of around 1 min[6]), no transfer function was assumed between the systemic circulation and the CNS. The effects of midazolam and 1-OHMDZ on the score were analysed by logistic regression analysis using SPSS version 10.0 (SPSS Inc., Chicago, USA). The success of the model in predicting score was tested using the chi-squared test on the number of correct scores predicted.

Results

The median age of the patients was 5 yr (range from 9 months to 12 yr), median weight was 21 kg (range 8–75 kg), and there were 22 females and 23 males. Midazolam dosage varied from 0.2 to 1.37 mg kg^{-1} (median 0.5 mg kg^{-1}). The timing of the first blood sample was between 20 and 122 min (median 49 min) and the second between 40 and 200 min (median 85 min) after dose.

Pharmacokinetics

Individual measured plasma midazolam concentrations (normalized for a dose of 100 μg kg^{-1}) are shown in Figure 2, along with the Bayesian model predictions of the full concentration–time profiles and the mean profile for the population. The profiles for patients who had extreme values for one or more PK parameters are highlighted. The goodness of fit of the model to the experimental data is indicated in Figure 3. The residual concentrations against time were scattered randomly about zero indicating no systematic error. The population parameter values for midazolam PK are summarized in Table 1.

Individual measured plasma 1-OHMDZ concentrations (normalized for a midazolam dose of 100 μg kg^{-1}) are shown in Figure 4, along with the model predictions of the full concentration–time profiles and the mean profile for the population. The best model was generated with log normal distributions for fm(1st), fm(sys), and k(1-OHMDZ). Predicted *vs* observed values for 1-OHMDZ concentrations are shown in Figure 5, and indicate the goodness of fit of the link model. The correlation between observed and predicted values for 1-OHMDZ was less than that for the parent drug. Similarly, the residual 1-OHMDZ concentration against time showed greater random scatter around zero than for parent drug, midazolam. However, no systematic error was apparent. The population parameter values for 1-OHMDZ are summarized in Table 1. It should be noted that, in the absence of information on the volume of distribution of 1-OHMDZ, the values of fm(1st) and fm(sys) are not

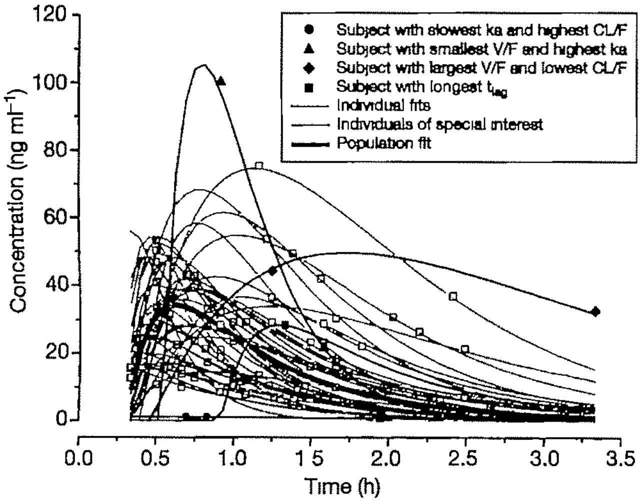


Fig 2 Individual (lines) and population (solid line) model fits to plasma midazolam concentrations following oral midazolam administration to 45 children (data are normalized for a 100 μg kg^{-1} dose).

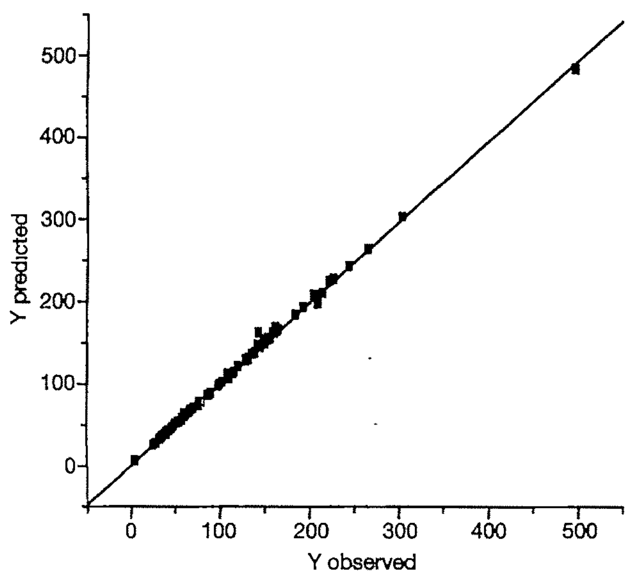


Fig 3 Relationship between plasma midazolam concentrations generated by the model (Y predicted) and those measured in individual patients (Y observed) (r^2=0.996).

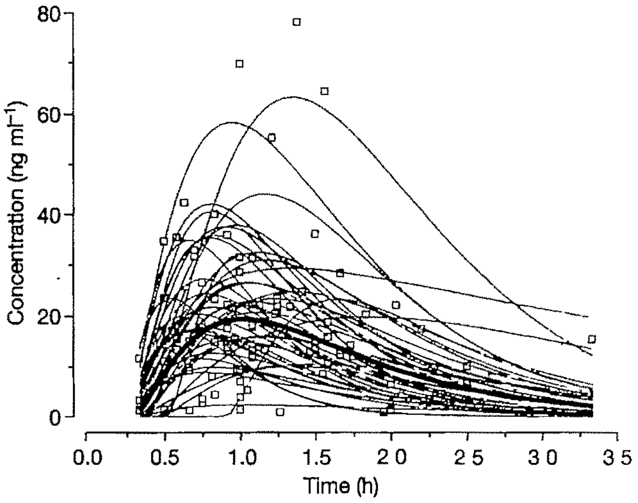


Fig 4 Individual (lines) and population (solid line) model fits to plasma 1-OHMDZ concentrations following oral midazolam administration to 45 children (data are normalized for a 100 μg kg^{-1} dose of midazolam)

Table 1 Median (upper and lower quartile) values of PK parameters for midazolam and 1-OHMDZ *CL/F*=oral clearance, *V/F*=volume of distribution, ka=absorption rate constant, t_{lag}=absorption lag time, kel=elimination rate constant for midazolam, fm(sys)=proportion of 1-OHMDZ generated from the systemic circulation, fm(1st)=proportion of 1-OHMDZ produced from the first-pass metabolism of midazolam, and k(1-OHMDZ)=elimination rate constant for 1-OHMDZ

CL/F **(litre kg^{-1} h^{-1})**	***V/F*** **(litre kg^{-1})**	**ka (h^{-1})**	**t_{log} (h)**	**kel (h^{-1})**	**fm(sys)**	**fm(1st)**	**k(1-OHMDZ)**
2 56 (1.90–4 04)	2.2 (1 9–3.8)	6 11 (3.94–9 43)	0 29 (0 26–0.32)	1.41 (1.16–1 81)	0 269 (0 187–0 374)	0.178 (0 140–0.214)	3 02 (2 58–3 51)

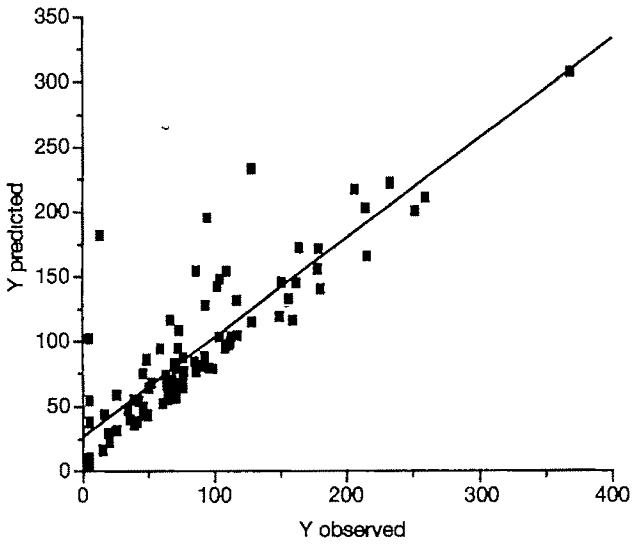


Fig 5 Relationship between plasma 1-OHMDZ concentrations generated by the model (Y predicted) and those measured in individual patients (Y observed) (r^2=0.94)

Table 2 Co-variate analysis by stepwise multiple regression ($F \geq 5$). *CL/F*=oral clearance, *V/F*=volume of distribution, ka=absorption rate constant, and MR_{AUC}=metabolic ratio

Kinetic parameter	Co-variable	% Variation explained
CL/F	MR_{AUC}	84
V/F	Propofol	9
ka	Propofol, thiopentone	16

identifiable. However, their ratio is. Accordingly it can be calculated that 37% of exposure to 1-OHMDZ is related to the metabolite formed during the first-pass metabolism of midazolam.

Co-variates for PK parameters

Stepwise multiple regression analysis ($F \geq 5$) of the co-variables revealed a number of correlations as summarized in Table 2. The MR was directly related to *CL/F* and accounted for 84% of the variability in oral midazolam clearance. Propofol administration was inversely correlated with *V/F* and directly with ka. The latter was also correlated with thiopental administration. There were no significant co-variables for the metabolite PK parameters.

Weight, age, and sex were not significant co-variables for weight-corrected oral midazolam clearance, weight-corrected volume of distribution, ka or t_{lag}. The data for weight-corrected midazolam oral clearance were also analysed independently by weight assuming no effects from other co-variables. This relationship is shown in Figure 6. The change in clearance with body weight (BW) was best described by a non-linear function:

$$[(CL/F)/BW=7.73*BW^{-0\ 37}].$$

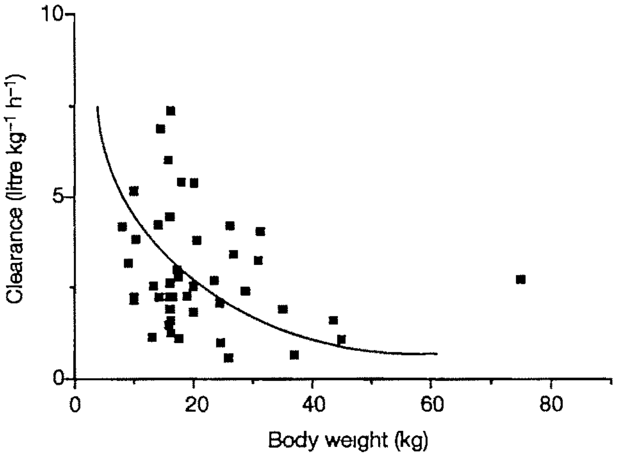


Fig 6 Relationship between weight-normalized oral clearance of midazolam and body weight in 45 children (r^2=0 063; P=0 1)

However, the r^2 value (0.063) did not reach statistical significance (P=0.10).

Pharmacodynamics

Twenty-eight patients had scores recorded at the same time as the first blood sample as follows: score 1=11, score 2=17. Neither patient characteristics nor PK parameters were different between the 28 patients where a sedation score was recorded and the remaining 17 out of 45 patients where no score was recorded. Results of the logistic regression analysis of score in relation to plasma midazolam concentration alone and score and plasma 1-OHMDZ concentration alone are shown in Figure 7A and B, respectively. The combined influence of midazolam and 1-OHMDZ concentration on score is shown in Figure 8.

The logistic regression PK-PD models were compared using the –2 log likelihood values. A number of additional co-variables (age, weight, and MR) were introduced into the PK-PD analysis in order to ascertain the most parsimonious model. The results are summarized in Table 3. The prediction of score from 1-OHMDZ alone appeared to be a slightly better than for midazolam alone, but inferior to the model that assumed midazolam and 1-OHMDZ together contribute to the sedative effect. Age, weight, and MR were not significant co-variates in the PD analysis. The regression curves in Figure 8 give the probability of a response at a given drug/metabolite concentration. As seen in Figure 8, higher plasma concentrations of both midazolam and 1-OHMDZ increase the probability of a higher sedation score.

According to the parameter values derived from the logistic regression analysis describing the influence of midazolam (0.021) and 1-OHMDZ (0.048) on sedation score, it appears that 1-OHMDZ has a greater potency than midazolam. However, after considering the higher unbound fraction of 1-OHMDZ (0.106) *vs* midazolam (0.024),[6] the

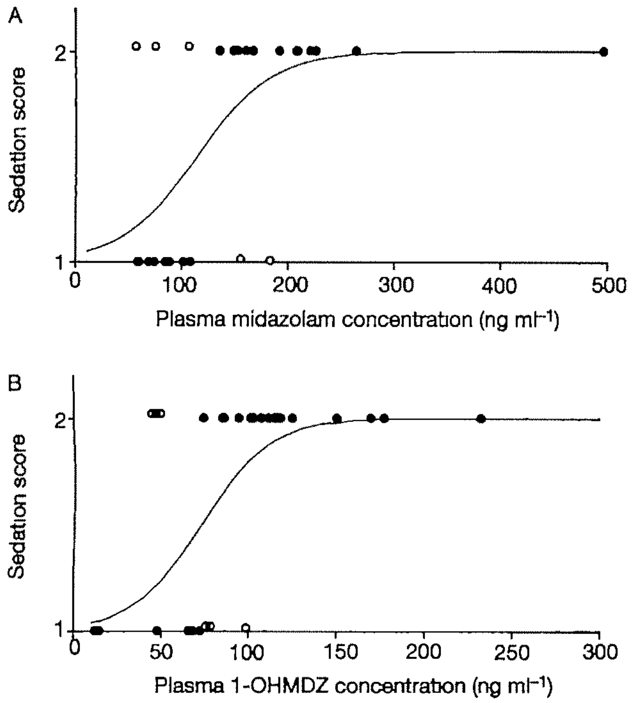


Fig 7 Observed sedation score (symbols) and predicted probability of score (line) with respect to plasma concentration of (A) midazolam and (B) 1-OHMDZ Closed symbols indicate those patients for whom the model successfully predicted score.

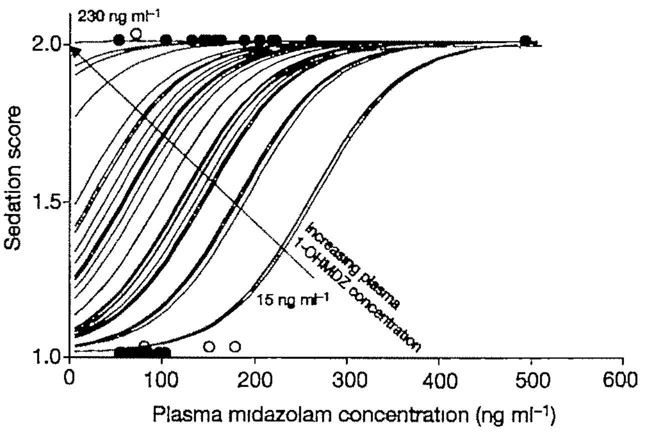


Fig 8 Observed sedation score (symbols) and predicted probability of score (line) with respect to plasma concentrations of both midazolam and 1-OHMDZ. Closed symbols indicate those patients for whom the model successfully predicted score

Table 3 Comparison of the logistic regression models. Score=sedation score

Model	−2 LL
Score and midazolam	26.25
Score and 1-OHMDZ	24.25
Score and midazolam+1-OHMDZ	20.04

relative potency of midazolam was calculated to be 1.9 times that of 1-OHMDZ.

Overall, the PK-PD model predicted the correct sedation score successfully in 86% of cases (P=0.01 and P=0.05 for scores 1 and 2, respectively). For the observed average plasma concentrations of 150 ng ml^{-1} (midazolam) and 90 ng ml^{-1} (1-OHMDZ) the odds ratio was 4 in favour of score 2 *vs* 1. A simulation based on the PD parameters showed that a 50% increase in the current mean dose (from 0.5 to 0.75 mg kg^{-1}) would result in an odds ratio of 275 in favour of score 2.

Discussion

The random nature of the sampling times in this study necessitated the use of sparse data analysis. Sparse data analysis from as few as 20–30 patients may be sufficient to perform a reasonable population PK study provided that the sampling times are not fixed but random.[16 17] This methodology is well suited to clinical practice as it reduces the inconvenience to patients, particularly neonates and children and can thus be considered more ethical.

The previous applications of population-PK analysis to midazolam have used a two-compartment model to fit i.v. data from neonates in intensive care.[8 18] Within the confines of the present study a one-compartmental model was sufficient and produced the best fit. It is a common observation that following oral administration of many drugs that display multi-compartment characteristics after i.v. injection, a single compartmental model is observed. This is because the absorption phase overlaps with the distribution phase.[19] Our population PK estimates for midazolam using sparse data population PK analysis were in broad agreement with those from other paediatric studies where more intensive blood sampling was performed (Table 4). The estimated oral clearance in our study (2.7 litre kg^{-1} h^{-1}) was higher than values recorded in adult studies of between 0.51 and 1.2 litre kg^{-1} h^{-1}.[10 24]

Despite large variations between individual patients, predicted plasma midazolam concentrations from the final model were very close to the actual data. This large inter-patient variation was consistent with the observations of Marshall and colleagues.[3] The variability could not be explained by concurrent drug therapy or disease state but a direct relationship between MR and midazolam oral clearance was established. The latter was expected as the MR is a reasonably robust measure of gut and liver CYP3A activity. Rogers and colleagues[25] found that MR values derived from concentrations at 60 min after dosage explain 46% of the variability of midazolam clearance, and Lin and colleagues[26] found that a 4 h plasma MR could explain between 80 and 91% of the inter-individual variability in the area under the curve of midazolam. Our median sample time was 70 min and we were able to explain 84% of the variability in *post hoc* estimates of oral midazolam clearance. In another study in 20 children, de Wildt and

Table 4 Clearance, volume of distribution, and elimination half-life of midazolam in children *Estimated from i.v clearance assuming an oral bioavailability of 0.27 CL/F=oral clearance, V/F=volume of distribution, and $t_{1/2}$=elimination half-life

Study	Age range (yr)	CL/F (litre kg^{-1} h^{-1})	V/F (litre kg^{-1})	$t_{1/2}$ (h)	Route
Present	9 months to 12 yr	2.7 (1.5)	2.2 (1.5)	0.5 (0.45)	Oral
Tolia and colleagues[20]	6–18	2.2 (1.1)*	2.2 (0.4)*	0.75 (0.4)	i.v.
Payne and colleagues[1]	3–10	3.5 (1.2)	1.3 (0.6)	1.2 (0.3)	Oral
de Wildt and colleagues[13]	3–16	2.0 (1.6)*	4.0 (4.4)*	2.5 (2.3)	i.v
Jones and colleagues[21]	5–9	3.4 (0.7)*	–	1.8 (0.5)	i.v
Rey and colleagues[22]	1–5	–	–	2.4	i.v.
Reed and colleagues[23]	6 months to 15 yr	2.3 (1.1)	11 (5.5)	3.5	Oral
Carrillo and colleagues[10]	Adults	0.51 (0.18)		2.39 (0.9)	Oral

Table 5 Reported variability in hepatic and intestinal CYP3A content *Relative units **From quantitative PCR analysis (transcripts per microgram of total RNA) All intestinal data are normalized per unit of villin

Study	*n*	Mean expression (pmol (mg protein)$^{-1}$)	SD	Range	Fold difference
Liver					
Shimada and colleagues[27]	30	96	51		
Shimada and colleagues[28]	8	77	34	37.8–143.0	3.8
Guengerich and colleagues[29]*	36	248	37		
Snawder and colleagues[30]	40	142	105	19.7–440.0	22.3
Gentest Corp (Pelkonen and colleagues)[31]	12	109	20		
Iribarne and colleagues[32]	20	2.3*	1.2	0.4–4.9	10.2
Forrester and colleagues[33]	12				60
Transon and colleagues[34]	42				13
Iyer and colleagues[35]	21				18
Intestine					
Taipalensuu and colleagues[36]	13	1.4	0.3	0.8–1.8	2.2**
Paine and colleagues[37]	20	30.6 (duodenum)		3.0–91	30.3
		22.6 (jejunum)		2.1–91	43.2
Johnson and colleagues[38]	74	10.8	4.85	1.3–23	19

colleagues[13] failed to show a relationship between MR and midazolam clearance, although there was a correlation between MR and age.

Assuming that MR is a valid marker of CYP3A4 activity, a 10-fold inter-individual variability was observed within the children that we studied. This is in agreement with the majority of values reported in the literature (Table 5). The variability measured in MR observed after oral administration of midazolam reflects variability in both gut and hepatic CYP3A4, which appear to be independently regulated.[39] Inspection of our previous data on the development of enterocytic CYP3A4 in children,[38] indicates an 11-fold range in expression in biopsy samples from 48 children aged 1.25–12 yr (19 female). This is again in good agreement with the range of variability observed in MR.

The correlations between propofol and *V*/*F* and propofol/thiopental and ka, albeit low, are difficult to explain and may be spurious. Although propofol can decrease the systemic clearance of midazolam by 30–40%,[40] no effect was detected in this study as the first sample was taken before administering propofol. Age and weight were not significant co-variates of weight-adjusted oral midazolam clearance. Two previous studies have found no age-related changes in midazolam weight-corrected clearance.[13,41] Another study performed in a paediatric intensive care setting has shown a decreased weight-corrected midazolam clearance in children below 2 yr of age and an increased clearance from 3 yr.[9]

When analysed independently of other co-variables, weight-adjusted oral midazolam clearance appeared to decrease exponentially with body weight (Fig. 6); a trend also observed for other CYP3A4 substrates such as carbamazepine.[42] A recent study has also shown decreasing oral midazolam clearance with age in children 6 months to 16 yr old with age-related weight-adjusted clearance values comparable with our results.[23] The trend is confirmed by decreased oral midazolam clearance in adults.[10,24] An explanation for increased weight-normalized drug clearance in children of lower weight could be their greater liver volume relative to body weight. Thus, the liver represents 4% of the body in 1-yr-old children compared with 2.5% in adults.[43,44] This alone could account for a 1.5-fold increase in clearance in children. An alternative explanation could be a higher concentration of catalytically active CYP3A4 per gram liver weight in children. However, Blanco and colleagues[45] have shown that this is not the case. As oral midazolam is given at a standard dose of 0.5 mg kg^{-1} to children up to 30 kg body weight, younger children may be underdosed, although this may be partly offset by increased plasma concentrations of 1-OHMDZ in these patients.

While Blumer [46] considers that 1-OHMDZ shows only minimal biological activity, there is overwhelming evidence against this notion.[5 6 47–49] Indeed our results indicate that at the same plasma concentrations 1-OHMDZ contributes 1.9-fold more to sedation than midazolam. However, after considering the 4-fold higher unbound fraction of 1-OHMDZ in plasma[6] the relative potency of 1-OHMDZ compared with midazolam decreased to 0.5. Thus, high oral midazolam clearance (resulting in the formation of the less active 1-OHMDZ metabolite) coupled with a decreased benzodiazepine receptor density in younger infants[50] may lead to therapeutic failure in some paediatric patients.

According to our analysis, about 37% of the 1-OHMDZ formed appeared to be generated during the first-pass of parent drug through the gut wall and liver. Thummel and colleagues[24] in a cross-over study of both intravenous and oral midazolam PK in 20 healthy adults, showed that both liver and gut contributed equally to the first-pass metabolism each removing 40% of available parent drug. The low value for first-pass generation of 1-OHMDZ in this study could be a result of lower intestinal expression of enterocytic CYP3A4 and subsequent intestinal first-pass in some of the younger children.[38] Higher weight-adjusted liver volume in children[43 44] will have a disproportionate effect on the systemic (liver alone) compared with the first-pass production of 1-OHMDZ (sum of gut and liver). Therefore, the relative value for the proportion of metabolite generated on first-pass calculated from fm(1st)/(fm(1st)+fm(sys)) will be reduced.

The separate i.v. administration of active metabolites, such as 1-OHMDZ, is the gold standard technique for assessing the *in vivo* activity relative to parent compound. However, these studies are difficult to justify in children. Other approaches include inhibition of the metabolic pathway that is responsible for the formation of the metabolite,[51 52] or investigation of the pharmacological effect in sub-populations who are genetically deficient with respect to the biotransformation pathway that produces the active metabolite.[53] Alternatively, PK-PD modelling, based on either inter-individual or intra-individual differences in the plasma concentration–time profiles of parent drug and metabolite, can be used without disruption of drug metabolism or the use of phenotypic groups. We have used such an approach to estimate the contribution of dihydromorphine to the analgesic effect of dihydrocodeine,[14] and now extend it to assessing the relative sedative activity of midazolam and 1-OHMDZ.

In developing the PD model we omitted a delay function between concentrations in plasma and the effect compartment (CNS). However, it has been shown that this transfer half-life for both midazolam and 1-OHMDZ is very short (0–5 min)[6 54 55] and will not have a significant impact on the 2-level sedation endpoint. A similar logistic regression model for sedation score was recently applied to data for adult patients receiving a continuous i.v. infusion of midazolam.[56] However, the latter study failed to account for the effects of active metabolites.

For the 28 patients who were assigned a sedation score after administration of midazolam, 11 patients had a score of 1 (awake) and 17 a score of 2 (drowsy/asleep). Previous reports on response rates to similar oral midazolam doses have related the effects to ablation of anxiety.[3 57–59] Our scoring system was not directly comparable with those used in these reports as the authors combined all patients who were asleep, drowsy, or awake but not anxious to form one single group of 'patients with some response'. These reports indicated a response rate of between 80 and 90%, albeit response varying from being calm to asleep.[3 57–59] By subdividing score 1 from our records into those who were anxious (n=2) and those who were calm (n=9) it appears that an overall 93% (26/28) achieved some type of response in our study. This is entirely consistent with previous reports.[3 57–59]

Higher scores correlated significantly with higher plasma concentrations of midazolam and 1-OHMDZ, in agreement with the findings of Marshall and colleagues.[3] Nevertheless, if the aim is not to have any patients fully awake before the start of the operative procedure then a 50% increase in current dosage might be required. This would increase the odds ratio from 4 to 275 in favour of score 2 (drowsy, asleep).

Children often present with anxiety pending an invasive procedure, and require rapid sedation without the discomfort of i.v. administration. Accordingly, oral midazolam is the agent of choice used by many paediatric anaesthetists. However, a current issue with oral midazolam is the lack of a licensed formulation for oral administration to children, although a cherry flavoured formulation has recently been evaluated for use in the USA (Versed Syrup, Roche Laboratories Inc., Nutley, NJ). This has been assessed in a multi-centre randomized, double-blind, parallel group, dose ranging trial and found to be effective in sedating 80% of patients within 30 min.[3] Although an oral midazolam preparation is now commercially available in the UK as a 'special', this does not have a product licence.

Acknowledgements

The assistance of the anaesthetic and nursing staff at Sheffield Children's Hospital involved in the collection of blood samples is gratefully acknowledged. This work was supported by grant S/F/0763 from Action Research

References

1 Payne K, Mattheyse FJ, Liebenberg D, Dawes T. The pharmacokinetics of midazolam in paediatric patients. *Eur J Clin Pharmacol* 1989; **37**: 267–72

2 Malinovsky JM, Populaire C, Cozian A, Lepage J-Y, Lejus C. Premedication with midazolam in children. Effects of intranasal, rectal and oral routes on plasma midazolam concentrations. *Anaesthesia* 1995, **50**: 351–4

3 Marshall J, Rodarte A, Blumer J, Khoo KC, Akbari B, Kearns G. Pediatric pharmacodynamics of oral midazolam syrup. *J Clin Pharmacol* 2000; **40**: 578–89

4 Smith MT, Eadie MJ, O'Rourke Brophy T. The pharmacokinetics of midazolam in man. *Eur J Clin Pharmacol* 1981; **19**: 271–8

5 Ziegler WH, Schalch E, Leishman B, Eckert M. Comparison of the effects of intravenously administered midazolam, triazolam and their hydroxy metabolites. *Br J Clin Pharmacol* 1983; **16**: 63S–9S

6 Mandema JW, Tuk B, van Steveninck AL, Breimer DD, Cohen AF, Danhof M. Pharmacokinetic-pharmacodynamic modeling of the central nervous system effects of midazolam and its main metabolite α-hydroxymidazolam in healthy volunteers. *Clin Pharmacol Ther* 1992; **51**: 715–28

7 Jacqz-Aigrain E, Daoud P, Burtin S, Maherzi S, Beaufils F. Pharmacokinetics of midazolam during continuous infusion in critically ill neonates. *Eur J Clin Pharmacol* 1992; **42**: 329–32

8 Burtin P, Jacqz-Aigrain E, Girard P, *et al.* Population pharmacokinetics of midazolam in neonates. *Clin Pharmacol Ther* 1994; **56**. 615–25

9 Hughes J, Gill AM, Mulhearn H, Powell E, Choonara I. Steady state plasma concentrations of midazolam in critically ill infants and children. *Ann Pharmacother* 1996; **30**: 27–30

10 Carrillo JA, Ramos SI, Agundez JAG, Martinez C, Benitez J. Analysis of midazolam and metabolites in plasma by high performance liquid chromatography: probe of CYP3A. *Ther Drug Monit* 1998; **20**: 319–24

11 Dampster AP, Laird NM, Rubin DB. Maximum likelihood from incomplete data via the EM algorithm *J Roy Stat Soc B* 1977; **39**: 1–38

12 Mentre F, Gomeni G. A two step iterative algorithm for estimation in nonlinear mixed effect models with an evaluation in population pharmacokinetics. *J Biopharm Stat* 1995; **5**: 141–58

13 de Wildt SN, Riva L, van der Anker JN, Murray DJ. Does age alter the pharmacokinetics of midazolam and 1-OH-midazolam in paediatric patients? *Clin Pharmacol Ther* 2000; **67**: 104

14 Webb JA, Rostami-Hodjegan A, Abdul-Manap R, Hofmann U, Mikus G, Kamali F. Contribution of dihydrocodeine and dihydromorphine to analgesia following dihydrocodeine administration in man: a PK-PD modeling analysis. *Br J Clin Pharmacol* 2001; **52**: 35–43

15 Yamaoka K, Nakagawa T, Uno T. Application of Akaike's information criteria (AIC) in the evaluation of linear pharmacokinetic equations. *J Pharmacokin Biopharm* 1976; **6**: 165–75

16 Breant V, Charpiat B, Sab JM, Maire P, Jelliffe RW. How many patients and blood levels are necessary for population pharmacokinetic analysis. *Eur J Clin Pharmacol* 1996; **51**: 283–8

17 Lee PID. Design and power of a population pharmacokinetic study. *Pharm Res* 2001; **18**: 75–82

18 Lee TC, Charles BG, Harte GJ, Gray PH, Steer PA, Flenady VJ. Population pharmacokinetic modeling in very premature infants receiving midazolam during mechanical ventilation. *Anesthesiology* 1999; **90**: 451–7

19 Gibaldi M, Perrier D. Multicompartmental models. *Pharmacokinetics*, 2nd Edn. New York: Marcel Dekker, 1982: 83–111

20 Tolia V, Brennan S, Aravind MK, Kauffman RE. Pharmacokinetic and pharmacodynamic study of midazolam in children during esophagogastroduodenoscopy. *J Pediatr* 1991; **119**: 467–71

21 Jones RD, Visram AR, Chan MM, *et al.* A comparison of three induction agents in paediatric anaesthesia–cardiovascular effects and recovery. *Anaesth Intens Care* 1994; **22**: 545–55

22 Rey E, Delaunay L, Pons G, *et al.* Pharmacokinetics of midazolam in children: comparative study of intranasal and intravenous administration. *Eur J Clin Pharmacol* 1991; **41**: 355–7

23 Reed MD, Rodarte A, Blumer JL. The single-dose pharmacokinetics of midazolam and its primary metabolite in pediatric patients after oral and intravenous administration. *Pediatrics* 2001; **41**: 1359–69

24 Thummel KE, O'Shea D, Paine MF, *et al.* Oral first pass elimination of midazolam involves both gastrointestinal and hepatic CYP3A-mediated metabolism. *Clin Pharmacol Ther* 1996; **59**: 491–502

25 Rogers JF, Nafziger AN, Kashuba ADM, *et al.* Prediction of midazolam (MDZ) clearance (CL) using minimised sampling (MS) of 1-OHM and 1-OHM/MDZ in healthy subjects (HS). *Clin Pharmacol Ther* 2000; **69**: 89

26 Lin YS, Lockwood G, Brian W, *et al.* *In vivo* phenotyping for CYP3A by a single-point determination of midazolam plasma concentration *Drug Metab Rev* 2001; **33**: 97

27 Shimada T, Yamazaki H, Mimura M, Inui Y, Guengerich FP. Interindividual variations in human liver cytochrome P-450 enzymes involved in the oxidation of drugs, carcinogens and toxic chemicals: studies with liver microsomes of 30 Japanese and 30 Caucasians. *J Pharmacol Exp Ther* 1994; **270**: 414–23

28 Shimada T, Tsumura F, Yamazaki H. Prediction of human liver microsomal oxidations of 7-ethoxycoumarin and chlorzoxazone with kinetic parameters of recombinant cytochrome P-450 enzymes. *Drug Metab Dispos* 1999; **27**: 1274–80

29 Guengerich FP, Turvy CG. Comparison of levels of several human microsomal cytochrome P-450 enzymes and epoxide hydrolase in normal and disease states using immunochemical analysis of surgical liver samples. *J Pharmacol Exp Ther* 1991; **256**: 1189–94

30 Snawder JE, Lipscomb JC. Interindividual variance of cytochrome P450 forms in human hepatic microsomes: correlation of individual forms with xenobiotic metabolism and implications in risk assessment. *Reg Toxicol Pharmacol* 2000; **32**: 200–9

31 Pelkonen O, Myllynen P, Taavitsainen P, *et al.* Carbamazepine: a 'blind' assessment of CVP-associated metabolism and interactions in human liver-derived *in vitro* systems. *Xenobiotica* 2001; **31**. 321–43

32 Iribarne C, Berthou F, Baird S, *et al.* Involvement of cytochrome P450 3A4 enzyme in the N-demethylation of methadone in human liver microsomes. *Chem Res Toxicol* 1996; **9**: 365–73

33 Forrester LM, Henderson CJ, Glancey MJ, *et al.* Relative expression of cytochrome P450 isoenzymes in human liver and association with the metabolism of drugs and xenobiotics. *Biochem J* 1992; **281**. 359–68

34 Transon C, Lecoeur S, Leeman T, Beaune P, Dayer P. Interindividual variability in catalytic activity and immunoreactivity of three major human liver cytochrome P450 isozymes. *Eur J Clin Pharmacol* 1996, **51**: 79–85

35 Iyer KR., Sinz MW. Characterization of Phase I and Phase II hepatic drug metabolism activities in a panel of human liver preparations. *Chem-Biol Interact* 1999; **118**: 151–69

36 Taipalensuu J, Tornblom H, Lindberg G, *et al.* Correlation of gene expression of ten drug efflux proteins of the ATP-binding cassette transporter family in normal human jejunum and in human intestinal epithelial Caco-2 cell monolayers. *J Pharmacol Exp Ther* 2001; **299**: 164–70

37 Paine MF, Khalighi M, Fisher JM, *et al.* Characterization of interintestinal and intraintestinal variations in human CYP3A-dependent metabolism. *J Pharmacol Exp Ther* 1997; **283**: 1552–62

38 Johnson TN, Tanner MS, Taylor CJ, Tucker GT. Enterocytic CYP3A4 in a paediatric population: developmental changes and the effects of coeliac disease and cystic fibrosis. *Br J Clin Pharmacol* 2001; **51**: 451–60

39 Lown KS, Ghosh M, Watkins PB. Sequences of intestinal and hepatic cytochromes P450 3A4 cDNAs are identical. *Drug Metab Dispos* 1998; **26**: 185–7

40 Hamaoka N, Oda Y, Ichiro H, *et al.* Propofol decreases the clearance of midazolam by inhibiting CYP3A4: an *in vivo* and *in vitro* study. *Clin Pharmacol Ther* 1999; **66**. 110–7

41 Wells TG, Ellis EN, Casteel HB. Pharmacokinetics of a single dose midazolam in children. *Clin Pharmacol Ther* 1991; **49**: 160

42 Summers B, Summers RS. Carbamazepine clearance in paediatric epilepsy patients. *Clin Pharmacokinet* 1989; **17**: 208–16

43 Murry DJ, Crom WR, Reddick WE, Bhargava R, Evans WE. Liver volume as a determinant of drug clearance in children and adolescents. *Drug Metab Dispos* 1995, **23**: 1110–6

44 Noda T, Todini T, Watanabe Y, Yamamoto S. Liver volume in children measured by computer tomography. *Pediat Radiol* 1997; **27**. 250–2

45 Blanco JG, Harrison PL, Evans WE, Relling MV. Human cytochrome P450 maximal activities in pediatric versus adult liver. *Drug Metab Dispos* 1999, **28**: 379–82

46 Blumer JL. Clinical pharmacology of midazolam in infants and children. *Clin Pharmacokinet* 1998; **35**: 37–47

47 Tuk B, van Oostenbruggen MF, Herben VM, Mandema JW, Danhof M Characterization of the pharmacodynamic interaction between parent drug and active metabolite in vivo: midazolam and alpha-OH-midazolam. *J Pharmacol Exp Ther* 1999; **289**: 1067–74

48 Hotz MA, Ritz R, Linder L, Scollo-Lavizzari G, Haefeli WE. Auditory and electroencephalographic effects of midazolam and alpha-hydroxy-midazolam in healthy subjects. *Br J Clin Pharmacol.* 2000; **49**: 72–9

49 Crevoisier C, Ziegler WH, Eckert M, Heizmann P. Relationship between plasma concentration and effect of midazolam after oral and intravenous administration. *Br J Clin Pharmacol* 1983; **16** (Suppl 1): 51S–61S

50 Reichelt R, Hofmann D, Fodisch HJ, Mohler H, Knapp M, Hebebrand J. Ontogeny of the benzodiazepine receptor in human brain, fluorographic, immunochemical and reversible binding studies. *J Neurochem* 1991; **57**: 1128–35

51 Heiskanen T, Olkkola KT, Kalso E. Effects of blocking CYP2D6 on the pharmacokinetics and pharmacodynamics of oxycodone. *Clin Pharm Ther* 1998; **64**: 603–11

52 Abul-Manap A, Wright CE, Gregory A, *et al* The antitussive effect of dextromethorphan in relation to CYP2D6 activity. *Br J Clin Pharmacol* 1999; **48**: 382–7

53 Eckhardt K, Li S, Ammon S, Schanzle G, Mikus G, Eichelbaum M. Same incidence of adverse drug events after codeine administration irrespective of the genetically determined differences in morphine formation. *Pain* 1998; **76**. 27–33

54 Dingemanse J, van Gerven JM, Schoemaker RC, *et al* Integrated pharmacokinetics and pharmacodynamics of Ro 48-6791, a new benzodiazepine, in comparison with midazolam during first administration to healthy male subjects. *Br J Clin Pharmacol* 1997; **44**: 477–86

55 Mould DR, DeFeo TM, Reele S, *et al.* Simultaneous modeling of the pharmacokinetics and pharmacodynamics of midazolam and diazepam. *Clin Pharmacol Ther* 1995; **58**: 35–43

56 Barr J, Zomorodi K, Bertaccini EJ, Shafer SL, Geller E. A double-blind, randomized comparison of IV lorazepam versus midazolam for sedation of ICU patients via a pharmacologic model. *Anesthesiology* 2001; **95**· 286–98

57 Saarnivaara L, Lingren L, Klemola UM. Comparison of chloral hydrate and midazolam by mouth as premedicants in children ungergoing otolaryngological surgery. *Br J Anaesth* 1988, **61**: 390–6

58 Parnis SJ, Foate JA, Van der Walt JH, Short T, Crowe CE. Oral midazolam is an effective premedication for children having day stay anaesthesia. *Anaesth Intens Care* 1992; **20**. 9–14

59 McMillan CO, Spahr-Schopfer IA, Sikich N, Hartley E, Lerman J. Premedication of children with oral midazolam. *Can J Anaesth* 1992; **39**: 545–50

60 *Medicines for Children* London, Royal College of Paediatrics and Child Health Publications Ltd, 1999

British Journal of Anaesthesia 89 (3): 438–41 (2002)

Pharmacokinetics of 0.75% ropivacaine and 0.5% bupivacaine after ilioinguinal–iliohypogastric nerve block in children[†]

T. I. Ala-Kokko[1]*, J. Karinen[2], E. Räihä[2], K. Kiviluoma[2] and S. Alahuhta[2]

[1]Departments of Anaesthesiology and Pharmacology and Toxicology, University of Oulu and [2]Department of Anaesthesiology, Oulu University Hospital, Oulu, Finland

**Corresponding author: Department of Anaesthesiology, Oulu University Hospital,*
PO Box 21, FIN-90029 OUH, Oulu, Finland

Background. Blockade of the ilioinguinal and iliohypogastric nerves is a useful procedure in paediatric patients undergoing inguinal surgery. Bupivacaine 2 mg kg^{-1} has been recommended for this block. We compared the plasma concentrations of ropivacaine and bupivacaine following an ilioinguinal–iliohypogastric block.

Methods. Forty children scheduled for elective inguinal surgery were randomized to receive 2 mg kg^{-1} of either 0.75% ropivacaine or 0.5% bupivacaine. Surgical anaesthesia was maintained with mask inhalation of oxygen, nitrous oxide and sevoflurane. Venous blood samples were drawn at regular intervals for up to 2 h and plasma was separated. Total venous plasma concentrations were determined by gas chromatography.

Results. The groups were similar with respect to age, weight and dose of local anaesthetic. The peak plasma concentration achieved was significantly higher in the bupivacaine group compared with the ropivacaine group (2.2 *vs* 1.2 μg ml^{-1}, *P*=0.025). The time to peak plasma concentration was significantly shorter in the bupivacaine group (24 *vs* 35 min, *P*=0.024). The initial distribution half time of bupivacaine was significantly shorter (3.6 *vs* 6.5 min, *P*=0.020) compared with that of ropivacaine.

Conclusions. Bupivacaine is more rapidly absorbed from the injection site and leads to higher plasma concentrations than ropivacaine.

Br J Anaesth 2002; **89**: 438–41

Keywords: anaesthesia; anaesthetic techniques, epidural; anaesthetics local, bupivacaine; anaesthetics local, ropivacaine

Accepted for publication: April 18, 2002

Ropivacaine is the first *S*-enantiomer aminoamide local anaesthetic in clinical use. It has been found to cause less cardiac and central nervous system toxicity than bupivacaine.[1–3] Blockade of the ilioinguinal and iliohypogastric nerves with bupivacaine is a useful procedure that provides postoperative analgesia in paediatric patients undergoing inguinal surgery.[4] Bupivacaine 2 mg kg^{-1} has been recommended for this block. Ropivacaine has been previously used in paediatric patients for caudal block.[5–11]

There are some physicochemical differences between ropivacaine and bupivacaine. They have almost identical dissociation constants, but ropivacaine is marginally less tightly bound to plasma proteins and its apparent lipid solubility is approximately half of that of bupivacaine.[12–14] Plasma levels of bupivacaine and ropivacaine in children have been previously compared following caudal administration.[5 8] There are no comparative data available on their plasma levels following an ilioinguinal–iliohypogastric block. This study was undertaken to compare the total venous plasma concentrations of similar doses of ropivacaine and bupivacaine following ilioinguinal–iliohypogastric blockade in children.

Methods

After written informed parental consent and approval by the Oulu University Hospital Ethics Committee, 40 ASA I children, aged 2–16 yr and scheduled for elective inguinal surgery, were enrolled to receive 2 mg kg^{-1} of either ropivacaine or bupivacaine. The children were premedi-

---

[†]The results have been presented at the Scandinavian Society of Anesthesiology and Intensive Care Medicine annual meeting in Tromssa, Norway, 2001.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Table 1 Patient characteristics in the two treatment groups. The data are expressed as mean (SD or range). The volume of local anaesthetic per kg of body weight was significantly higher in the bupivacaine group. $^{*}P = 0.006$ bupivacaine *vs* ropivacaine

Parameter	Bupivacaine (n=20)	Ropivacaine (n=20)
Age (yr)	5.9 (2.9–12.6)	7.6 (2.3–12.7)
Weight (kg)	23.7 (2.4)	27.5 (9.4)
Height (cm)	117.0 (17.0)	124.1 (16.9)
Volume of local anaesthetic per patient weight (ml kg^{-1})	0.39 (0.005)	0.29 (0.06)*

Table 2 Pharmacokinetic parameters following ilioinguinal–iliohypogastric blockade with bupivacaine or ropivacaine. The data are expressed as mean (SD). C_{max} = the maximum measured plasma concentration, T_{max} = time to the maximum measured concentration, $T\alpha$ = initial distribution half time, AUC = area under the concentration–time curve from 0–120 min, calculated from the individual concentration–time curves according to the trapezoid rule. A P-value of <0.05 is considered statistically significant

Parameter	Bupivacaine	Ropivacaine	P-value
C_{max} (μg ml^{-1})	2.2 (1.0)	1.5 (0.8)	0.025
T_{max} (min)	24 (11.9)	35.0 (15.4)	0.024
$T\alpha$ (min)	3.6 (1.8)	6.5 (4.4)	0.020
AUC (min μg ml^{-1})	189.6 (89.5)	115.3 (68.1)	0.025

cated with oral midazolam 0.4–0.5 mg kg^{-1} and randomly allocated to receive either 0.75% ropivacaine (Naropin, Astra, Finland) or 0.5% bupivacaine (Marcain, Astra, Finland). The administration of the local anaesthetic was not blinded. The treatment allocation codes were placed in sealed envelopes, and for each consecutive patient, the anaesthetist opened the next envelope in order.

The patients underwent ECG, end-tidal CO_2 concentration (E'_{CO_2}) monitoring, non-invasive arterial pressure measurements and pulse oximetry. In all cases, anaesthesia was maintained with sevoflurane and nitrous oxide in oxygen by facemask inhalation, with spontaneous ventilation.

After induction of anaesthesia, ilioinguinal–iliohypogastric nerve blockade was performed with a 22-gauge short bevelled needle. The local anaesthetic was injected at a point that was 1–2 cm medial and inferior to the superior anterior iliac spine under the fascia of the external oblique muscle. If the calculated volume of local anaesthetic was <4 ml, it was diluted with saline up to 4 ml. All blocks were performed by experienced paediatric anaesthetists (J.K., K.K.).

Venous blood samples of 5 ml were drawn for the determination of total drug concentrations at 2, 5, 10, 20, 30, 40, 50, 60 and 120 min after the dose. Care was taken not to exceed 5% of the estimated blood volume of the patient. The blood samples were immediately centrifuged at room temperature, and the plasma was separated and stored at −20°C until analysis.

The total concentrations of ropivacaine and bupivacaine bases in 1 ml of plasma were measured by gas chromatography.[15] All samples were measured in duplicates with intra-pair variations (SD) of 4.0 (3.0)% and 3.4 (3.5)% for ropivacaine and bupivacaine, respectively.

The peak measured plasma concentration (C_{max}) and the time to reach C_{max} (T_{max}) were estimated from the individual observed plasma concentration time profiles. The initial distribution and elimination half-lives were calculated from the linear phases of the semilogarithmic concentration–time curves. The area under the concentration–time curve (AUC) was calculated from the individual concentration–time curves according to the trapezoid rule.[16] Differences between the groups were compared by the Mann–Whitney test, with a P-value of <0.05 considered statistically significant. The SPSS for Windows statistical package was used.

Results

Patient characteristics were similar in the two groups (Table 1). By chance, children in the ropivacaine group were slightly taller than those in the bupivacaine group. The volume of local anaesthetic used per kg of body weight was higher in the bupivacaine group (0.39 *vs* 0.29 ml kg^{-1}, P=0.006). Dilution was required for only one patient in the ropivacaine group. The peak plasma concentration achieved was significantly higher in the bupivacaine group (2.2 *vs* 1.5 μg ml^{-1}, P=0.025) (Table 2). The time to the peak plasma concentration was significantly shorter in the bupivacaine than in the ropivacaine group (24 *vs* 35 min, P=0.024). The initial distribution half time of bupivacaine was also significantly shorter (3.6 *vs* 6.5 min, P=0.020) compared with that of ropivacaine. The mean AUC from 0–120 min for bupivacaine was larger than that for ropivacaine (189.6 *vs* 115.4 min μg ml^{-1}, P=0.025). At all time points, the plasma concentrations of bupivacaine were higher than those of ropivacaine (Fig. 1). No opioid analgesics were needed during the anaesthesia in either group.

Discussion

The concentrations of local anaesthetics used in this study were those used in routine clinical practice in our hospital. Ilioinguinal–iliohypogastric nerve blockade with similar doses of 0.75% ropivacaine and 0.5% bupivacaine resulted in higher peak plasma concentrations and more rapid absorption of bupivacaine than ropivacaine. The volume of bupivacaine injected per kg of body weight was 1.5 times higher than that of ropivacaine. In addition to the total dose of local anaesthetic injected, the rate of absorption is related to the vascularity of the injected area, the concentration of local anaesthetic used and the volume of the space into which the injection is made. The higher volumes of bupivacaine injected into the inter-fascial space partly

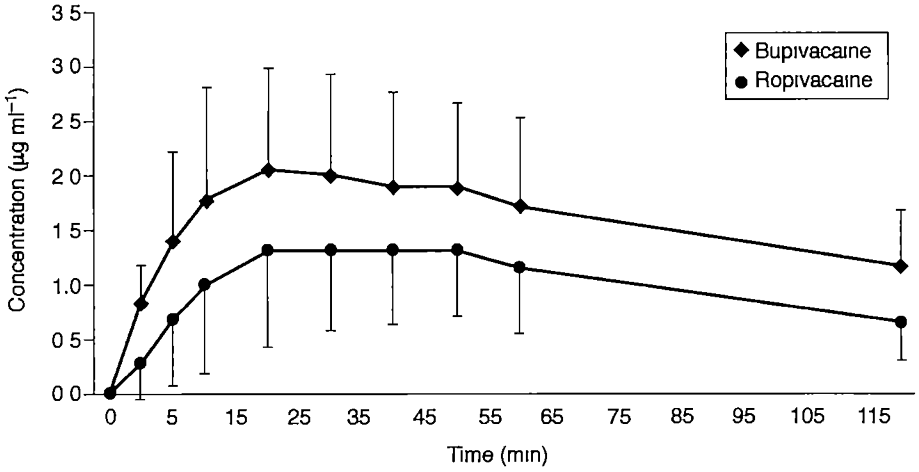


Figure 1 Mean (SD) venous plasma concentrations of bupivacaine (n=20) and ropivacaine (n=20) after ilioinguinal–iliohypogastric blockade in children. At 120 min, there were samples from 19 patients in both the ropivacaine and the bupivacaine groups The mean AUC for bupivacaine is significantly larger than that for ropivacaine.

explain the higher bupivacaine concentrations obtained. Although the concentration of ropivacaine administered was higher, the plasma concentrations observed were lower than those of bupivacaine at the higher absorption rate of bupivacaine. This may be further explained by the higher lipid solubility of bupivacaine.

Maximum total venous plasma concentrations of >2 µg ml^{-1} were achieved in 60% of the children in the bupivacaine group and 30% in the ropivacaine group. These concentrations of bupivacaine and ropivacaine are close to the reported maximum tolerated venous plasma concentrations of 2.1 µg ml^{-1} and 2.2 µg ml^{-1}, respectively, as evaluated from i.v. administration to healthy volunteers.[3] A 'full dose' of 2 mg kg^{-1} is probably not necessary for an ilioinguinal–iliohypogastric block, and further studies with efficacy data are required to determine the minimum dose required. Although the mean peak plasma concentration in the bupivacaine group was lower than the generally accepted safe maximum total plasma concentration of 4 µg ml^{-1}, a peak concentration of 4.9 µg ml^{-1} of bupivacaine was observed in one child.[17] Such a high concentration may suggest that at least part of the injection might have inadvertently been administered intravascularly. However, no adverse effects were noted in any of the children in this study. It should be pointed out, however, that possible seizure activity may have been masked by the general anaesthesia, which is known to increase the threshold for seizures.

There are only limited data available on bupivacaine concentrations following ilioinguinal–iliohypogastric blockade. In previous studies, lower mean peak plasma bupivacaine concentrations of 0.79 µg ml^{-1} and 1.35 µg ml^{-1} have been reported.[18 19] In the study by Stow and colleagues,[18] however, a lower dose of bupivacaine (1.25 mg kg^{-1}) was used. In the study by Epstein and coworkers,[19] a dose of 2 mg kg^{-1} of 0.25–0.5% bupivacaine was used, and their study series included younger and smaller children than those in our study. Furthermore, both unilateral and bilateral blocks were induced in their study. There were only eight patients who received unilateral blocks induced with 0.5% bupivacaine similar to those used in our study. Although the volume of local anaesthetic per kg of body weight was similar to ours, the mean peak plasma concentration of bupivacaine was lower (1.45 µg ml^{-1}) than that measured in our study. They observed a peak plasma concentration of 2.3 µg ml^{-1} in one patient. This could be explained by the fact that there is generally wide inter-individual variation between the plasma concentrations of local anaesthetics as well as their pharmacokinetic variables.[20] Our series of 20 patients included eight patients with a peak plasma concentration of bupivacaine lower than 2 µg ml^{-1}. In these patients, the mean peak plasma concentration was 1.3 µg ml^{-1}, which is similar to that found in the study of Epstein and colleagues.[19]

In contrast to ilioinguinal–iliohypogastric blockade, equal peak plasma concentrations of bupivacaine and ropivacaine have been measured following a caudal block.[8] This has been explained by the lower rate of systemic absorption of bupivacaine from the caudal space. Furthermore, the concentrations of bupivacaine and ropivacaine measured in the present study were three times and twice as high, respectively, than those following caudal block.[8] In addition, the times to the peak plasma concentration were shorter for both bupivacaine and ropivacaine than those following a caudal block. It has been shown with bupivacaine that absorption from the caudal space is slower and results in lower plasma concentrations than following ilioinguinal–iliohypogastric blockade.[18] The absorption rates at different sites of injection are known to be directly related to local blood flow and inversely related to local tissue binding.[21] The intrinsic vasoconstrictive effect of ropivacaine may slow down its absorption from the injection site while, in contrast, the vasodilative effect of bupivacaine enhances absorption.[22 23] It has been shown that plasma uptake is faster from more vascular areas, such as the intercostal space or the axilla, compared with the caudal space.[21 24] A previous study showed that, due to its higher lipid solubility, bupivacaine is more intensively absorbed locally into the caudal space, preventing its systemic absorption.[8] Injection into the narrow inter-fascial space may enhance systemic absorption and partly explain the higher plasma concentrations of both ropivacaine and bupivacaine compared with those following injection into the caudal space.

In conclusion, ilioinguinal–iliohypogastric blockade with 2 mg kg^{-1} of 0.5% bupivacaine led to a more rapid absorption and higher plasma concentrations than a similar dose of 0.75% ropivacaine. Furthermore, the rate of absorption and the peak plasma concentrations of both drugs were higher than those reported following caudal block.

Acknowledgement

The technical assistance of Mrs M. Luukkonen (Department of Pharmacology and Toxicology) in performing the drug analysis is appreciated.

References

1 Markham A, Faulds D. Ropivacaine: a review of its pharmacology and therapeutic use in regional anaesthesia. *Drugs* 1996; **52**: 429–49

2 McClure JH Ropivacaine. *Br J Anaesth* 1996; **76**: 300–07

3 Knudsen K, Beckman M, Suurkula M, Blomberg S, Sjovall J, Edvardsson N. Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers. *Br J Anaesth* 1997; **78**: 507–14

4 Shandling B, Steward DJ Regional analgesia for postoperative pain in pediatric outpatient surgery. *J Pediatr Surg* 1980; **15**: 477–80

5 Da Conceicao MJ, Coelho L Caudal anaesthesia with 0.375% ropivacaine or 0 375% bupivacaine in paediatric patients *Br J Anaesth* 1998; **80**· 507–8

6 Da Conceicao MJ, Coelho L, Khalil M Ropivacaine 0.25% compared with bupivacaine 0.25% by the caudal route. *Paediatr Anaesth* 1999; **9**· 229–33

7 Ivani G, Mereto N, Lampugnani E, *et al.* Ropivacaine in paediatric surgery: preliminary results. *Paediatr Anaesth* 1998; **8**· 127–9

8 Ivani G, Lampugnani E; Torre M, *et al.* Comparison of ropivacaine with bupivacaine for paediatric caudal block *Br J Anaesth* 1998; **81**: 247–8

9 Ala-Kokko TI, Partanen A, Karinen J, Kiviluoma K, Alahuhta S. Pharmacokinetics of 0.2% ropivacaine and 0 2% bupivacaine following caudal blocks in children *Acta Anaesthesiol Scand* 2000; **44**: 1099–102

10 Koinig H, Krenn CG, Glaser C, *et al.* The dose-response of caudal ropivacaine in children. *Anesthesiology* 1999; **90**· 1339–44

11 Lonnqvist PA, Westrin P, Larsson BA, *et al.* Ropivacaine pharmacokinetics after caudal block in 1–8 year old children *Br J Anaesth* 2000; **85**: 506–11

12 Rosenberg PH, Kytta J, Alila A. Absorption of bupivacaine, ethidocaine, lignocaine and ropivacaine into n-heptane, rat sciatic nerve and human extradural and subcutaneous fat. *Br J Anaesth* 1986; **58**: 310–4

13 Åkerman B, Hellberg I-B, Trossvik C. Primary evaluation of the local anaesthetic properties of the amino amide agent ropivacaine (LEA 103) *Acta Anaesthesiol Scand* 1988; **32**: 571–8

14 Lee A, Fagan D, Lamont M, Ticker G T, Halldin M, Scott DB. Disposition kinetics of ropivacaine in humans. *Anesth Analg* 1989; **69**: 736–8

15 Huha T, Ala-Kokko TI, Salomaki T, Alahuhta S Clinical efficacy and pharmacokinetics of 1% ropivacaine and 0 75% bupivacaine in peribulbar anaesthesia for cataract surgery. *Anaesthesia* 1999, **54**: 137–41

16 Matthews JNS, Altman DG, Lampbell MJ, Royston P. Analysis of serial measurements in medical research *Br Med J* 1990, **300** 230–5

17 Moore DC, Balfour RI, Fitzgibbons D Convulsive arterial plasma concentrations of bupivacaine and the response to diazepam therapy. *Anesthesiology* 1979; **50**: 454–6

18 Stow PJ, Scott A, Phillips A, White JB. Plasma bupivacaine concentrations during caudal analgesia and ilioinguinal–iliohypogastric nerve block in children. *Anaesthesia* 1988; **43**: 650–3

19 Epstein RH, Larijani GH, Wolfson PJ, Ala-Kokko TI, Boerner TF Plasma bupivacaine concentrations following ilioinguinal–iliohypogastric nerve blockade in children. *Anesthesiology* 1988; **69**· 773–6

20 Burm AGL, De Boer AG, Van Kleef JW, *et al.* Pharmacokinetics of lidocaine and bupivacaine and stable isotope labelled analogues. a study in healthy volunteers. *Biopharm Drug Dispos* 1988; **9**: 85–95

21 Tucker GT. Pharmacokinetics of local anaesthetics. *Br J Anaesth* 1986; **58**: 717–31

22 Kopacz DJ, Carpenter RL, Mackey DC. Effect of ropivacaine on cutaneous capillary blood flow in pigs. *Anesthesiology* 1989, **71**: 69–74

23 Geradini G, Samuelson U, Jernbeck J, Aberg B, Sjostrand N Comparison of vascular effects of ropivacaine on isolated rings of human arteries. *Acta Anaesthesiol Scand* 1995; **39**: 765–8

24 Tucker GT, Mather LE Pharmacokinetics of local anaesthetic agents. *Br J Anaesth* 1975, **48**: 213–24

British Journal of Anaesthesia **89** (3). 442–5 (2002)

Evaluation of S1 motor block to determine a safe, reliable test dose for epidural analgesia

Z. Daoud[1], R. E. Collis[2]*, B. Ateleanu[2] and W. W. Mapleson[2]

[1]Anaesthetic Department, Memorial Hospital, Darlington DL3 6HX, UK. [2]Anaesthetic Department, University Hospital of Wales and University of Wales College of Medicine, Cardiff CF14 4XW, UK
**Corresponding author*

Background. Accidental intrathecal injection of bupivacaine during epidural analgesia in labour remains a hazard, with the potential to cause total spinal anaesthesia and maternal collapse. Sacral block appears early after intrathecal injections compared with epidural ones, and we therefore used S1 motor block to determine a safe and reliable test dose for epidural catheter misplacement.

Methods. Mothers booked for elective Caesarean section were given various intrathecal doses of bupivacaine with fentanyl during routine combined spinal–epidural anaesthesia.

Results. Using sequential allocation we found that the ED_{50} for S1 motor block 10 min after intrathecal injection was bupivacaine 7 mg with fentanyl 14 µg (95% CI, 6.2–7.8 mg). We then used intrathecal bupivacaine 13 mg to look for the ED_{95}. We found the calculated $ED_{97.5}$ to be bupivacaine 9.7 mg with fentanyl 19.4 µg (95% CI, 8.7–11.4).

Conclusion. We conclude that testing for S1 motor block 10 min after epidural injection of bupivacaine 10 mg is a reliable test to detect accidental intrathecal injection in the obstetric population.

Br J Anaesth 2002; **88**: 442–5

Keywords: anaesthesia, obstetric; anaesthetic techniques, epidural; anaesthetic techniques, test doses; anaesthetics local, bupivacaine; spinal cord, motor block

Accepted for publication: March 6, 2002

The accidental intrathecal injection of bupivacaine during epidural analgesia in labour remains a hazard, with the potential to cause total spinal anaesthesia and maternal collapse. The main features, which are said to distinguish between epidural and intrathecal injection, are rapid analgesia, excessive sensory block, early sacral block, intense motor block and hypotension in the latter. There have been no specific tests that have been shown to reliably differentiate between the two sites of administration.

This study was designed to evaluate the use of S1 motor block as a reliable and easily reproducible clinical sign that will differentiate between an epidural injection and an accidental subarachnoid injection for labour analgesia.

We used S1 motor block as our clinical test because during epidural anaesthesia there is a sequence of motor blockade, starting with an early lumbar motor block involving hip flexion, and then extending to a sacral motor block involving the plantar flexion of the foot. In spinal anaesthesia, early sacral anaesthesia is characteristic. In other words, S1 blockade appears early after an intrathecal injection and is the last dermatome to be affected after an epidural injection. Yarnell and colleagues[1] showed that after 10 ml of 0.25% bupivacaine, only 3% of mothers had S1 motor blockade.

Methods

With full local research ethics committee approval and patient written informed consent, we recruited mothers who were booked for elective Caesarean section at term with a singleton foetus. The anaesthetic technique was a combined spinal epidural (CSE). Exclusion criteria included maternal refusal, contraindications to regional technique, multiple pregnancy and complicated medical history including pregnancy-induced hypertension.

I.v. access and routine monitoring were established in the anaesthetic room. The non-invasive arterial pressure cuff was set for a 2-min recording cycle. I.v. fluids were infused before and during the anaesthetic (Hartmann's solution 500–1000 ml).

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Table 1 Assessment of motor block A study responder was motor block of the ankle grade 2 or 3 (significant weakness of ankle plantar flexion) at 10 min SLR, straight leg raise

Grade of motor block	Hip movement	Ankle movement
0	Normal	Normal
1	Can SLR against a small downward pressure	Can plantar flex foot against some resistance
2	Cannot SLR against any downward pressure	Cannot plantar flex foot against resistance
3	No ability to SLR	No plantar flexion

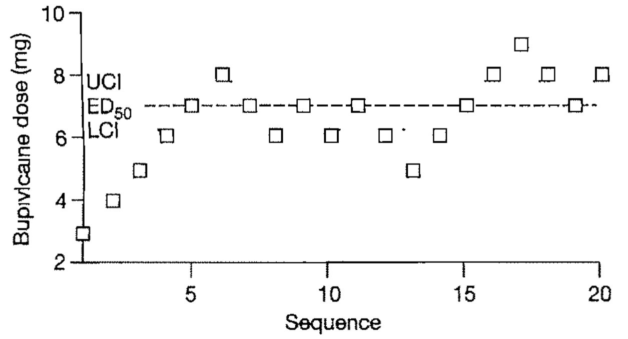


Fig 1 Responders and non-responders for S1 motor block after intrathecal bupivacaine showing the ED_{50} with the 95% confidence limits

The CSE technique was performed in the sitting position at the L3-4 interspace, a standard 16 gauge Tuohy needle was inserted into the epidural space using loss of resistance to air and a 119 mm 27 gauge Becton-Dickinson pencil-point spinal needle was inserted through the epidural needle once the epidural space was located After injection of the study mixture, the spinal needle was withdrawn and the epidural catheter was inserted. The Tuohy needle was then removed and the mother placed in the full right lateral position. After 5 min, the block was assessed and the mother turned supine with a 15° left lateral tilt. At 10 min, the block was tested again.

The loss of resistance to air was used to increase the reliability of detecting that the intrathecal dose was injected into the subarachnoid space, rather than being misplaced in the epidural space. The CSE technique had to be technically perfect with free flow of cerebrospinal fluid seen at the first pass of the spinal needle and no spillage of the spinal anaesthetic on injection, for the patient to remain in the study.

Arterial pressure was monitored non-invasively on a 2-min cycle and ephedrine was used in 6-mg i.v. boluses if the mother felt light-headed or nauseous or if her arterial pressure fell by 20% from her pre-block base line.

The study was divided into two parts. The first part was to determine the ED_{50} of S1 motor block, 10 min after spinal injection. The drugs used were 0.25% bupivacaine with fentanyl in a fixed ratio of bupivacaine 1 mg to fentanyl 2 µg. We chose this drug combination to mimic the bupivacaine–fentanyl mixture that is in common use as an epidural solution for labour analgesia. The first patient in the study was given intrathecal bupivacaine 3 mg with fentanyl 6 µg. At 10 min there was no S1 motor block (non-responder), and the next patient in the study received 4 mg and so on until the next patient did have S1 motor block (responder) (Table 1). The next patient after a responder received bupivacaine 1 mg and fentanyl 2 µg less, while the next patient after a non-responder received bupivacaine 1 mg and fentanyl 2 µg more. From this up–down sequential allocation, the ED_{50} for S1 motor block at 10 min was calculated after 20 patients.

After the 10-min initial study period, the assessor decided if the block was adequate for Caesarean section. An adequate block was considered to be a T4-S1 temperature block and a T6-S1 light touch block, together with a dense motor lumber–sacral block. If the block was inadequate, increments of 0.5% bupivacaine 5 ml were injected into the epidural space at 5-min intervals until a satisfactory block was obtained, and epidural morphine 4 mg given for postoperative analgesia.

The plan for the second part of the study was to use a fixed dose equal to roughly twice the ED_{50}, derived from part one of the study, in 60 patients. The choice of twice the ED_{50} was based on the rule-of-thumb that sensitivity to injected drugs amongst the population ranges from half the ED_{50} to twice the ED_{50}. The number 60 was chosen on the grounds that if *r* patients did not respond, where *r* was zero or very small, the upper 95% confidence limit of non-responders[2] would be between approximately *r*+3 and *r*+6 out of 60, i.e. an uncertainty of 5–10%. In fact, 62 mothers were given bupivacaine 13 mg (plain 0.5% bupivacaine with 26 µg of fentanyl) using the CSE technique. We chose 13 mg rather than 14 mg because we did not want to deviate too far from our routine practice of bupivacaine 12.5 mg and fentanyl 25 µg for elective Caesarean section. S1 motor block was assessed at 10 min, as before. Epidural morphine was given for postoperative analgesia.

Results

Applying the formula of Dixon and Massey[3] to the 20 patients in the first part of the study showed that the ED_{50} for S1 motor block at 10 min was bupivacaine 7.0 mg with fentanyl (95% CI, 6.2–7.8) (Fig. 1).

In the second part of the study all the 62 patients given bupivacaine 13 mg with fentanyl had S1 motor block 10 min

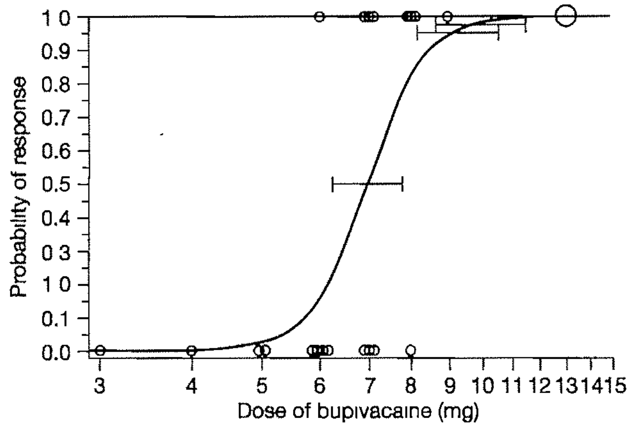


Fig 2 Probability of response (S1 motor block at 10 min after bupivacaine with fentanyl) against dose on a logarithmic scale Circles represent individual patients, with the circles at probability 0 being 'no response' and those at 1 being 'response' The largest circle represents the 62 patients receiving a 13-mg dose. The curve is the fitted logistic regression Error bars are the 95% confidence limits of the ED_{50}, ED_{95} and $ED_{97.5}$

after intrathecal injection. Therefore, on the basis of those patients alone, the estimated incidence of non-responders to a dose of 13 mg is 0 with an upper 95% confidence limit[2] of 3.6 in 62 patients i.e. a 2.5% risk that 6% of patients will not respond to 13 mg.

Logistic regression analysis[4 5] of the results for all 82 patients made use of all the data. This confirmed the Dixon Massey result, ED_{50} being 7.0 mg (95% CI, 6.2–7.8) with an estimated ED_{95} of 9.1 mg (95% CI, 8.2–10.6) and $ED_{97.5}$ of 9.7 mg (95% CI, 8.7–11.4) (Fig. 2).

Differences between the characteristics of the blocks and haemodynamic stability were seen after the two parts of the study. Statistical analysis was not performed because the groups were not randomized and are of unequal size. The data from patient number one has also been excluded from this part of the analysis, as she required ephedrine 39 mg following the smallest intrathecal dose of bupivacaine 3 mg, by far the largest dose of ephedrine of any patient in any part of the study.

Fifty per cent of mothers in the first part required ephedrine with an average dose of 13.6 mg, whilst 75% of mothers in the second part of the study required on average 17.3 mg. Nine of 10 mothers who developed hypotension in part one of the study, did so after the spinal injection and then tended to need more ephedrine during the epidural top-ups to maintain arterial pressure. Only one mother needed a small 6-mg dose of ephedrine after her epidural top-up; she did not require ephedrine after her intrathecal injection. A wide dose range of epidural 0.5% bupivacaine was given to supplement the intrathecal injection (0–25 ml (0–125 mg)), and the mean time to establish the final block height was 25 min (range 15–50 min).

There were no excessive sensory blocks at final block assessment just before surgery commenced in the first part of the study, where a maximum intrathecal dose of bupivacaine 9 mg was used, followed by incremental epidural top-ups. There was, however, an 8% incidence of a sensory block to ice at C6 or above, and a 14% incidence of block to light touch at T2 and above, in part two of the study where only the higher dose intrathecal injection was given (Table 2).

Table 2 Haemodynamic results and block characteristics of the first and second parts of the study

	Part 1 (*n*=20)	**Part 2** (*n*=62)
Mothers requiring ephedrine (*n* (%))	10 (50)	46 (75)
Mean ephedrine use of those requiring ephedrine (mg)	13.6	17.3
Final block to ice: C6 or above (*n* (%))	0 (0)	5 (8)
Final block to light touch T2 or above (*n* (%))	0 (0)	9 (14.5)

Discussion

This study has determined a safe test-dose that can be used in the obstetric population to reliably detect, after 10 min, a top-up that was intended for the epidural space but has been given intrathecally. A combination of rapid sensory block, motor block, hypotension and analgesia has previously alerted anaesthetists to the possibility of accidental intrathecal injection, but the reliability and discrimination of these tests has never been determined, and neither has the best and most discriminative time period for making an evaluation been assessed. This study has looked at only one element i.e. S1 motor blockade, to allow reliable early detection. We found that there is a very steep dose response curve for S1 motor block and that bupivacaine 13 mg was in excess of the $ED_{97.5}$. There was also a significant incidence of high sensory blockade and hypotension using bupivacaine 13 mg, which could pose a problem if it occurred in a delivery room rather than theatre.

Historically, the test dose contained a mixture of low volume high dose local anaesthetic and a vasoconstrictor. The vasoconstrictor was used as an indicator of an accidental intravascular injection.[6] A vasoconstrictor has never been shown to be very predictive of an intravascular injection and careful aspiration of the epidural catheter has now taken its place. The high concentration, low volume local anaesthetic that has traditionally been used, aimed to identify an accidental subarachnoid block before a high volume, high concentration local anaesthetic was given into the epidural space.

It was suggested that an epidural test dose should be mandatory[7] and Kumar and colleagues[8] recommended the use of 1.5 ml of 0.5% bupivacaine (7.5 mg). Prince and colleagues[9 10] suggested 1.6 ml of 0.5% bupivacaine (8 mg) plus 10 min waiting time in order to avoid false negative tests. Others[11] recommended more than 10 yr ago that 10 ml of 0.125% bupivacaine (12.5 mg) is a safe and effective test dose. A review of the literature shows that obstetric anaesthetists use a wide range of test doses on initial epidural placement[12] and previous research has suggested a number of regimen ranging from 1.5% lidocaine 3 ml (45 mg) to 0.5% bupivacaine 3 ml (15 mg). No research has been able to demonstrate the safety and reliability profile of any of these regimen, or the exact test that should be performed.

It is now accepted that the main determinant of a so-called test dose is the actual dose of local anaesthetic injected in the epidural space. In other words, it has been shown that when injected intrathecally, 0.1% bupivacaine 10 ml (10 mg) results in the same spread and intensity as 2 ml of 0.5% bupivacaine (10 mg).[13] Therefore, the use of low volume, high concentration test doses are not necessary.

Another potential danger of epidural analgesia in labour is that accidental intrathecal injection has been reported many hours after an apparently uneventful epidural block. Obstetric anaesthetists use epidural boluses of 5–50 mg of bupivacaine for labour pain.[11] This wide range of doses would produce widely differing clinical pictures if the catheter migrated into the subarachnoid space. The use of 10-mg top-ups can therefore be recommended for use throughout labour as they give reliable analgesia[14] with a margin of safety. Routine assessment of the mother's ankle plantar flexion can be taught to anyone giving the top-ups, allowing early detection of catheter migration. We feel that it would remain a valuable test even if there were some hip flexion weakness.

A spin off from our study design was a comparison between low dose spinal anaesthetics followed by epidural top-ups and high dose spinal anaesthesia for Caesarean section. There was improved haemodynamic stability in the low dose group and fewer high blocks. The spinal blocks were easily supplemented by 0.5% epidural bupivacaine in the epidural space and in most cases there was only a few minutes increase in preparation time. We now use the low dose spinal anaesthetic technique with epidural top-ups, if reducing the risk of hypotension in the mother is important and there is no hurry to establish anaesthesia.

This study looked at only one element, i.e. S1 motor block, to allow reliable early detection of accidental intrathecal injection. Although we do not know what the incidence of S1 motor block is after bupivacaine 10 mg in the epidural space, we can assume it is very low as only 3% had S1 blockade after 25 mg of bupivacaine epidurally.[1] We found that there was a very steep dose response curve for S1 motor block. The $ED_{97.5}$ of 9.7 mg (95% CI, 8.7–11.4) approaches the result required for a reliable predictive test. Our initial guess of an ED_{95} from the ED_{50} of approximately double the dose of bupivacaine grossly over-estimated the result. Individual doses of 13 mg, used in the second part of the study, would be more reliable, but there was a high requirement for ephedrine with a high incidence of excessive sensory and motor blockade. We recognize that the addition of fentanyl may have altered our results and that bupivacaine alone may have a different $ED_{97.5}$, but we felt justified in our study design because an opioid is very commonly added to bupivacaine for labour analgesia.

We therefore recommend that epidural analgesia can be initiated with an epidural dose of bupivacaine 10 mg in a 0.1% concentration with fentanyl, followed by testing for S1 motor block at 10 min. Assessing the sensory spread of the block and the mother's arterial pressure also remains important. If the test dose is negative, the same dose can be used to establish and then maintain full analgesia in labour as required.

References

1 Yarnell RW, Ewing DA, Tiering E, Smith MH Sacralization of epidural block with repeated doses of 0.25% bupivacaine during labour. *Reg Anesth* 1990; **15**. 275–9

2 Davies OL, Goldsmith PL, eds *Statistical Methods in Research and Production*, 4th Edn. London· Longman Group, 1972, 445–7

3 Dixon WJ, Massey FJ jr. *Introduction to Statistic Analysis*, 4th Edn. Boston, MA· McGraw Hill, 1983; 426–41

4 Francis B, Green M, Payne C, eds *The GLIM System-Release 4 Manual*. Oxford: Clarendon Press, 1993

5 Healy MJR *GLIM: An Introduction*. Oxford: Clarendon Press, 1988

6 Mulroy M, Glosten B. The epinephrine test dose in obstetrics note the limitations. *Anesth Analg* 1998; **86**: 923–5

7 Morgan B. Is an epidural test dose mandatory? *Eur J Obstet Gynecol Reprod Biol* 1995, **59** (suppl): S57–8

8 Kumar CM, Dennison B, Panchal HI Epidural test dose *Anaesthesia* 1985, **40**. 1023

9 Prince G, McGregor D. Obstetric epidural test doses. A reappraisal. *Anaesthesia* 1986; **41**: 1240–50

10 Prince GD, Shetty GR, Miles M. Safety and efficacy of low volume extradural test dose of bupivacaine in labour. *Br J Anaesth* 1989; **62**. 503–40

11 Van Zundert A, Vaes L, Soetens M *et al.* Every dose given in epidural analgesia for vaginal delivery can be a test dose *Anesthesiology* 1987; **67**: 436–40

12 Burnstein R, Buckland R, Pickett JA A survey of epidural analgesia for labour in the United Kingdom. *Anaesthesia* 1999; **54**. 634–40

13 Vucevic M, Russell IF. Spinal anaesthesia for Caesarean section 0.125% plain bupivacaine 12 ml compared with 0.5% plain bupivacaine 3 ml. *Br J Anaesth* 1992; **68**. 590–595

14 Collis RE, Davies DW, Aveling W Randomised comparison of combined spinal-epidural and standard epidural analgesia in labour. *Lancet* 1995; **345**: 1413–16

British Journal of Anaesthesia 89 (3). 446–51 (2002)

Effect of thoracic epidural anaesthesia on colonic blood flow

T. H. Gould[1]*, K. Grace[2], G. Thorne[3] and M. Thomas[2]

[1]Sir Humphrey Davy Department of Anaesthesia, [2]University Department of Surgery and [3]University Department of Medical Physics, Bristol Royal Infirmary, Marlborough Street, Bristol BS8 2HW, UK

**Corresponding author*

Background. The effect of thoracic epidural block on splanchnic blood flow is unclear. It remains to be resolved if sympathetic block, increases or decreases regional splanchnic blood flow and whether regional splanchnic flow becomes dependent on cardiac output or perfusion pressure. A clear understanding of the regional haemodynamic consequences of an epidural block may modify practice with respect to epidural anaesthesia.

Methods. Fifteen patients, who underwent anterior resection for rectal cancer, had invasive intraoperative monitoring of arterial pressure, central venous pressure, cardiac output, inferior mesenteric artery flow (Doppler flow probe), and colonic serosal red cell flux (laser Doppler probe), while an epidural block was established with local anaesthetic. In three consecutive time periods, arterial pressure was first allowed to fall (to a mean arterial pressure of 60 mm Hg), then treated with colloid fluid resuscitation and finally by vasopressors until the pre-epidural arterial pressure had been restored.

Results. On induction of epidural block, there was a reduction in mean colonic serosal red cell flux to 65% and inferior mesenteric artery flow to 80% (mean) of pre-epidural levels. There was a strong association between mean arterial pressure and both measured inferior mesenteric artery blood flow ($P<0.004$) and colonic serosal red cell flux ($P<0.0001$). Changes in cardiac output were poorly associated with either inferior mesenteric artery blood flow ($P=0.638$) or colonic serosal red cell flux ($P=0.265$). Inferior mesenteric artery blood flow and colonic serosal red cell flux were restored to pre-epidural levels after arterial pressure had been improved with a vasopressor.

Conclusion. Once intraoperative epidural block has been established, colonic serosal red cell flux and inferior mesenteric artery flow are more closely associated with changes in mean arterial pressure than changes in cardiac output. The measured reduction in colonic flow does not respond to an increase in cardiac output with fluid resuscitation, but requires the use of a vasopressor to increase arterial pressure, before colonic blood flow is improved.

Br J Anaesth 2002; **89**: 446–51

Keywords: blood, flow, colonic; anaesthetic techniques, epidural

Accepted for publication: April 26, 2002

Three arteries from the aorta supply the gastrointestinal system in man: the coeliac artery supplies blood to the stomach, liver and spleen; the superior mesenteric artery supplies the entire small intestine and the right side of the colon; the inferior mesenteric artery delivers blood to the hindgut (distal colon and rectum). Typically, blood flow through these arteries is 20–25% of the cardiac output, but the distribution of blood flow within the tissue layers of the intestine is not uniform.[1] In unfed animals at rest, blood flow to the mucosal layer is 70–80% of total flow at the expense of the sub-mucosal, muscular, and serosal layers. After a meal, blood flow to the intestine increases by as much as 200%, and most of this increase is shifted to the mucosal layer by recruitment of previously closed capillaries.[1] The exact mechanism for this recruitment is unknown, but paracrine (e.g. vasoconstrictors—endothelin-1, platelet aggregating factor; vasodilators—endothelium-derived releasing factor, prostacyclin) and metabolic mediators (pH, Pa_{CO_2}, Pa_{O_2}) predominantly influence small vessels and hence may moderate changes in local mucosal flow. Larger vessels are under the influence of humoral (catecholamines, angiotensin II, vasopressin, serotonin)

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

and neural mediators (constriction; increased sympathetic, decreased parasympathetic tone and dilatation; decreased sympathetic tone and increased parasympathetic tone). These multifactorial control mechanisms are inter-related and the relative balance helps determine regional and local blood flow.

To understand and possibly manipulate splanchnic blood flow may be clinically useful. It has been suggested that vasodilatation of the splanchnic vascular bed will improve splanchnic blood flow.[2–4] This could be achieved by an injection of local anaesthetic into the thoracic epidural space, which would produce a dense sympathetic block (and a block of C and Aδ pain fibres). A fall in arterial pressure usually follows, concomitant with peripheral arterial and venous vasodilatation. Vasodilatation of the splanchnic vascular bed would be part of this response.

Epidural anaesthesia and analgesia are techniques commonly used in association with major surgery to improve patient outcome.[5] However, there are divergent views on the true effect of epidural block on splanchnic blood flow.[6–10] Previous studies have relied on only two or three single time point measures, and thus have failed to combine continuous measurement of splanchnic blood flow with real time changes in arterial pressure, central venous pressure, and cardiac output. Recent studies[8–10] have used the less invasive technique of gastric tonometry to measure gastric mucosal $P\text{CO}_2$ as an indirect assessment of splanchnic blood flow.

It is particularly difficult to study patients in the postoperative period with invasive techniques for splanchnic blood flow measurement. We therefore designed an intraoperative study to directly measure the changes in inferior mesenteric artery blood flow and colonic serosal red cell flux, resulting from the initiation of epidural anaesthesia and the subsequent manipulation of arterial pressure and cardiac output with fluid and vasopressors.

Patients and methods

Fully informed written consent was obtained from 15 patients (nine male, six female), age 46–85 yr (mean 66, median 72), who underwent anterior resection for rectal malignancy. This study was approved by the local ethics committee. Patients were excluded from the study if they had any pre-existing cardiovascular disease or were taking cardiovascular medication. All patients had 2 litres of normal saline with potassium chloride in the preoperative 18 h to replace the fluid loss that occurred with the bowel preparation before surgery.

After a standardized induction (propofol, fentanyl, atracurium) and maintenance of anaesthesia (ventilation, oxygen, air, isoflurane), an arterial line (for invasive arterial pressure monitoring), an internal jugular central venous catheter and a transoesophageal cardiac output probe (TECO1, Medicina) were inserted, followed by a thoracic epidural catheter at T9–10. Once surgery commenced, a laser Doppler probe (DRT4, Moor Instruments) was attached to the serosal surface of the sigmoid colon (to measure colonic serosal red cell flux) using a serosal suture and a Doppler ultrasound probe (OpDop) was positioned around the inferior mesenteric artery (to measure flow in the inferior mesenteric artery) following careful dissection of the artery and vein. From induction of anaesthesia to the beginning of the study, 1000 ml of Hartmanns solution was given to all patients. When all the monitors were in place and collecting data, the surgery was halted and the study commenced. The study composed of four consecutive time periods.

- Period 0: 5 min of steady-state physiological data were collected.
- Period 1: 0.5 mg kg^{-1} (6–8 ml) of 0.5% bupivacaine was then injected down the epidural catheter. Arterial pressure was allowed to fall to a mean arterial pressure of 60 mm Hg (systolic/diastolic approximately 95/50).
- Period 2: a rapid fluid infusion of gelofusin was then commenced fast enough to prevent the mean arterial pressure falling below 60 mm Hg. The infusion was stopped when the central venous pressure and cardiac output had both returned to at least pre-epidural levels.
- Period 3: up to three 2 mg bolus doses of methoxamine were then used over a 6–9 min period to return the arterial pressure to the pre-epidural level. Once this steady state had again been reached, data collection was terminated and surgery then completed.

Physiological measurements from the monitors were recorded for the duration of the study period (29–40 min).

The position of the probe for laser Doppler (DRT4, Moor Instruments) was adjusted to obtain the optimum signal strength and was then sutured onto the serosal surface of the bowel. Movement artifact is then eliminated by built-in software, which averages recorded values over 0.1 s time intervals. Continuous data of colonic serosal red cell flux was directly downloaded to a personal computer. During this study, red cell flux was measured continuously in 14 of the 15 patients. In one patient, data collection was unusable because of a failure of the event logging of therapeutic interventions.

The measurements of inferior mesenteric artery blood flow were recorded every 15 s and averaged to give a figure for each minute time point of the study. Complete data were collected for 11 patients of the 15 patients in the study. In two patients, difficulty was encountered obtaining an initial signal because of arterial spasm after manipulation of the vessel as it was dissected to attach the probe. In a further two patients, an inability to measure flow was thought to be a result of atheromatous disease.

Cardiac output data were averaged every six beats by the oesophageal Doppler and displayed. The data were stored within the software of the TECO1 and manually recorded at 1 min time point intervals. Heart rate, central venous pressure, systolic, diastolic, and mean arterial pressure were manually recorded at 1 min time point intervals contiguous with the other data throughout the study period.

The patient end tidal carbon dioxide (5–5.3 kPa) and end tidal isoflurane (0.8%) were maintained in all patients for the study period. Temperature was maintained at 36.5°C in all of the patients by use of heated under mattress and a heated over blanket, together with warming of i.v. fluids, commenced in the anaesthetic room.

The study design reflected the local management for the commencement of an epidural anaesthetic and the treatment of a subsequent fall in arterial pressure. The hospital ethical committee had granted approval for all aspects of this study.

Statistical analysis

The values for heart rate, central venous pressure, arterial pressure, cardiac output, colonic serosal red cell flux, and inferior mesenteric artery blood flow were all transformed to a percentage of the mean value obtained from the steady state 5 min in period 0. The transformation of the data to a percentage of the mean value in period 0 was made because of the variation between the 15 patients in the actual measured base line blood flow using the two techniques. Because of the difference between patients in the duration of each of the time periods, the data selected for analysis were the mean of the last 5 min of each of the study periods 0, 1, 2, and 3 for each physiological variable.

Multiple regression was used to explore the associations between the independent variables heart rate, central venous pressure, mean arterial pressure cardiac output and the dependant variables colonic mucosal serosal blood flow and inferior mesenteric artery blood flow. This analysis was performed using the robust regression option in Stata 7.0. Using this option the standard errors of the coefficients in the regression model are estimated using the Huber–White estimator of variance. This allows one to relax the assumption of the independence of the observations. That is to say a valid estimate of the standard errors is obtained even if the observations are correlated. The current analysis was conducted on the basis of the observations being clustered by patient (i.e. observations from the same patient were not assumed to be independent).

The 'robust multiple regression' was first performed for colonic serosal red cell flux (14 patients) with the variable heart rate, central venous pressure, mean arterial pressure, and cardiac output. A separate 'robust multiple regression' was then performed for inferior mesenteric artery flow (11 patients) with the same variables, because of the different number of completed patient data sets for each of the two measurements of flow.

This study was intended to be a pilot study of 20 patients. No power calculation was made because the changes in colonic blood flow were not predictable or consistent from previous studies.[3–10] Interim analysis showed consistent data, which were statistically significant after 15 patients.

Results

The median duration (95% confidence intervals (CI)) of period 0 was 5 min; period 1, 12 (8–16) min; period 2, 9 (5–13) min; and period 3, 8 (7–11) min.

The objectives of the study to manipulate mean arterial pressure, cardiac output, and central venous pressure as described in the method section were achieved. In period 1, mean arterial pressure fell to 60 mm Hg in all of the patients, 69% of the mean arterial pressure in period 0. At the end of period 2, cardiac output was 110% and central venous pressure was 107% of the values in period 0 in response to fluid therapy. The median (95% CI) volume of gelofusin given during period 2 for the 15 patients was 875 (700–1050) ml. At the end of period 3, in response to the vasopressor, central venous pressure had increased further, mean arterial pressure and cardiac output had returned to their pre-epidural levels. Of particular interest are the changes in colonic serosal red cell flux and inferior mesenteric artery blood flow measurements. In period 1, both measures of flow had a fall in association with the fall in mean arterial pressure. In period 2, there was minimal change in either flow measurement despite the increases in cardiac output and central venous pressure. Finally, in period 3, colonic serosal red cell flux and inferior mesenteric artery blood flow measurements increased with mean arterial pressure in response to the vasopressor (Figs 1 and 2).

It is clear from the multiple regression analysis that mean arterial pressure is the variable most closely associated with colonic serosal red cell flux (P<0.0001) (Table 1) and inferior mesenteric artery blood flow (P=0.004) (Table 2). Both colonic serosal red cell flux and inferior mesenteric artery blood flow are poorly associated with cardiac output (P=0.64, Table 1 and P=0.27, Table 2). There was one other significant association, inferior mesenteric artery flow with central venous pressure (P=0.015, Table 2). This could be accounted for by the continued increase in central venous pressure seen in period 3 in response to systemic vasoconstriction at the same time as there is an increase in inferior mesenteric artery flow.

Diagnostic tests were performed subsequent to the multivariate analysis, the residuals were found to be normally distributed and these values were found to be independent of the predicted values.

Although the results for arterial pressure have been presented as mean arterial pressure, similar associations exist for systolic and diastolic values.

Discussion

In previous published studies, splanchnic blood flow in patients is usually measured by indirect techniques which are then extrapolated to infer changes in actual blood flow. Methods commonly used are gastric tonometry (measures gradient between arterial and gastric mucosal Pa_{CO_2}), and

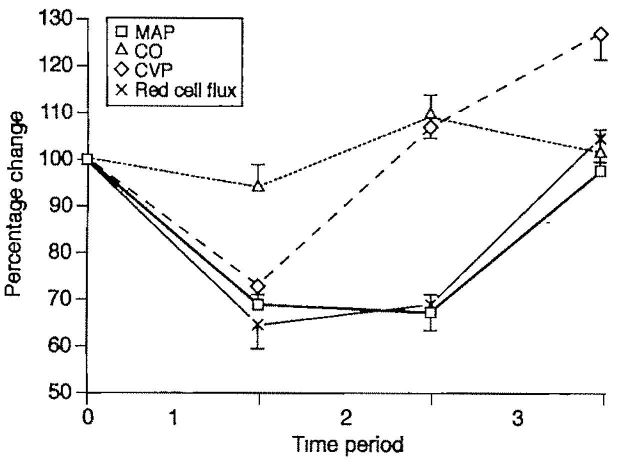


Fig 1 Graph of percentage change from period 0 for each parameter mean arterial pressure, cardiac output, central venous pressure, colonic serosal red cell flux (laser Doppler) at the end time points of periods 1, 2, and 3. Mean values, 95% CI.

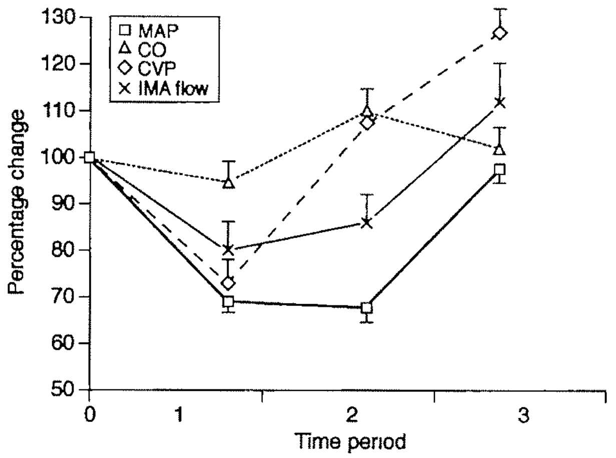


Fig 2 Graph of percentage change from period 0 for each parameter mean arterial pressure, cardiac output, central venous pressure, inferior mesenteric artery blood flow (OpDop) at the end time points of periods 1, 2, and 3. Mean values, 95% CI

indocyanine green (measures hepatic extraction of indocyanine green from the blood). Such indirect measurements have evolved principally because of the practical difficulties of using highly invasive direct techniques in patients. In conducting this study in the operating theatre on patients whose segment of bowel is later removed as part of the surgery, it was possible to use direct measurements of actual colonic blood flow.

The laser Doppler (DRT4, Moor Instruments) was used to measure colonic serosal red cell flux. When light is emitted into tissue that contains moving red blood cells, light is reflected from the stationary tissue and Doppler shifted light is reflected from the red blood cells. The shifted and unshifted light are collected on a photodetector and a beat frequency is generated. In reality, red blood cells move at different velocities and the back scattered light creates a spectrum of Doppler frequencies. The magnitude of the Doppler shift depends on the product of the number of moving cells and their velocity. This measured quantity is a true estimation of blood flow.[11–13] The relative changes in serosal and mucosal flows measured by laser Doppler are comparable[14] and hence placement of the probe onto the serosa is valid in this study design and technically easier and safer than mucosal measurements.

The Operative Doppler (OpDop: designed in the Department of Vascular Studies, Bristol Royal Infirmary) was used to measure directly flow in the inferior mesenteric artery. The diameter of the artery to be studied is measured and a 10 MHz pencil ultrasound probe is held in the appropriate size cuff against the vessel. Blood flow is calculated from the mean blood velocity and the vessel internal diameter (derived calibration factor to compensate for uneven insonation of the lumen). As reported previously, if the vessel diameter remains constant at the point of measurement, then the mean velocity is directly proportional to blood flow.[15 16]

The transoesophageal cardiac output probe (TECO1, Medicina) has undergone extensive validation studies. A probe 3 mm in diameter is inserted 35–40 cm into the distal oesophagus and is orientated to obtain the characteristic aortic flow signal. The area (integral) under each velocity—time waveform represents the stroke volume flowing in the descending aorta. Applying a nomogram that incorporates patient age, height, and weight enables an estimate of left ventricular stoke volume and hence cardiac output. Intraobserver variability is low and trend following is accurate over a wide range of flow and arterial pressure.[17 18] A recent study[19] highlighted the overestimation of cardiac output by oesophageal Doppler during lumbar epidural anaesthesia when compared with thermodilution techniques. The investigators in the present study were aware of this from our own preliminary work in preparation for this study. To choose the optimum measurement technique for cardiac output, oesophageal Doppler was compared with thermodilution in eight patients (over 18 months) in whom a pulmonary artery catheter was used for invasive cardiovascular monitoring at laparotomy. After commencement of thoracic epidural anaesthesia and adequate fluid resuscitation a measured increase in cardiac output occurred with both techniques. The increase was greater with the oesophageal method (which measures velocity of flow in the descending aorta), but less so than the magnitude reported by Leather and co-workers[19] who used an epidural placed at L2–3. The phenomenon is probably explained by a relative redistribution of flow between the upper and lower part of the body after the epidural was commenced and vasodilatation occurs. The investigators took the previously discussed observations into account, but selected the oesphageal Doppler, a much less invasive technique to measure cardiac output for the present study, as the main aim of the study was to observe the trend changes after the commencement of an epidural.

Table 1 Regression of robust standard errors of colonic serosal red cell flux (laser Doppler) with cardiac output, mean arterial pressure, heart rate, and central venous pressure

Colonic serosal red cell flux	**Coefficient (95% CI)**	***t* value**	***P*>[t]**
Cardiac output	–0.17 (–0.93, 0.59)	–0.48	0.638
Mean arterial pressure	10.2 (6.94, 13.55)	6.7	0.0001
Heart rate	–0.5 (–1.66, 0.64)	–0.94	0.362
Central venous pressure	0.93 (–3.23, 3.41)	0.06	0.952
Constant	63.62 (–41.94, 169.19)	1.3	0.216

Table 2 Regression of robust standard errors of inferior mesenteric artery blood flow (OpDop) with cardiac output, mean arterial pressure, heart rate, and central venous pressure

Inferior mesenteric artery blood flow	**Coefficient (95% CI)**	***t* value**	***P*>[t]**
Cardiac output	0.68 (–0.60, 1.96)	1.18	0.265
Mean arterial pressure	11.78 (4.87, 18.7)	3.8	0.004
Heart rate	–1.73 (–3.82, 0.36)	–1.84	0.095
Central venous pressure	–0.54 (–0.95, –0.13)	–2.95	0.015
Constant	144.8 (–5.3, 294.9)	2.15	0.057

The results of our intraoperative study demonstrate a strong association between colonic serosal red cell flux and inferior mesenteric artery flow with mean arterial pressure, when an epidural block has been established. The measured reduction in flow did not respond to an increase in cardiac output with fluid resuscitation but to an increase in vascular tone after the use of a vasopressor.

To understand the cardiovascular response to a change in vasomotor tone, it is useful to consider that arterial pressure is a function of flow (cardiac output) and the total resistance of the individual organ and tissue beds arranged in parallel. Efferent sympathetic tone of organ and tissue beds modifies internal flow resistance. The gradation of sympathetic tone (skin / skeletal muscle > kidney > intestine > brain > heart / lungs) is determined by the density of alpha receptors in the arterioles. Basal tone after a complete sympathetic block would be in the opposite direction, as tissues with the highest density of alpha receptors would be most affected. After epidural anaesthesia at the mid-thoracic level, there will be a loss of sympathetic tone, especially in the skeletal muscle below the level of the block. This loss of tone may lead to a 'steal' phenomenon away from the colonic bed and increased flow into the maximally dilated peripheral vascular beds.[20] At the same time the increase in venous capacitance will reduce cardiac end diastolic volume and cardiac output will normally fall. Any improvement in cardiac output (e.g. with i.v. fluid resuscitation) preferentially increases flow into the lower resistance vascular beds. In addition, the loss of vascular resistance in the peripheral vascular beds decreases the total arterio-venous pressure difference, arterial pressure falls and this may further reduce colonic blood flow.

How do the findings reported in this study correlate with the results from other studies that compare splanchnic blood flow after epidural anaesthesia–analgesia? An improvement in splanchnic blood flow has been recorded in a similar study using intraoperative laser Doppler flowmetry measured at the site of the colonic anastomosis[6] and in two studies with tonometry, one postoperative[9] the other in intensive care in septic patients.[10] Using tonometry, in a group of patients after aortic aneurysm surgery, investigators found no change in flow.[8] A further study[7] demonstrated results closest to our reported results, a fall in flow measured by an electromagnetic probe placed on the superior mesenteric artery. Flow then improved after dopamine $4\ \mu g\ kg^{-1}\ min^{-1}$. None of these studies[6–9] involved the combination of two direct invasive measurements of flow and such comprehensive data collection. Neither did the previously reported studies[6–9] control arterial pressure or manipulate fluid and vasopressors so tightly, compared with data presented in this study.

The variation in the reported studies is still confusing. The level of the epidural and the dose of bupivacaine did, however, vary between studies and in patients within the same study. The only study in addition to our reported results, where a thoracic epidural is placed consistently (T7–8 or T8–9), is the one which showed a fall in flow.[7] This is probably very important; indeed two animal studies,[21,22] (which use direct invasive measurement to measure blood flow) suggest that if the thoracic epidural is placed high (T1–5),[21] or a lumbar epidural is used,[22] sympathetic block is incomplete. Incomplete block may lead to increased sympathetic activity and a lesser decrease in arterial pressure, because baroreceptor stimulation produces increased splanchnic sympathetic activity and mesenteric venoconstriction.[22] Thus, as splanchnic tone is preserved, there is less change in arterial pressure and splanchnic blood flow is more stable.[22] An epidural placed in the mid-low thoracic region causes a decrease in sympathetic activity, mesenteric venodilatation,[23] a lower arterial pressure and reduced splanchnic blood flow.

The study procedure described in this manuscript was as relevant to clinical practice as possible, but the study is too small to show any detrimental side-effects from a reduction in colonic blood flow and was not designed to do so. Indeed, it is not really possible to take this study model much further because of the intraoperative time limitations and ethical considerations. Further studies with regard to the haemodynamic control of colonic blood flow should probably be pursued in an animal model. Adequate colonic blood flow is critical to gut mucosal integrity and anastomotic healing. A study of pHi using tonometry at the site of the anastomosis after anterior resection, showed a decrease in pHi after commencement of a thoracic epidural block and then improvement on its cessation.[23] It is also possible that a reduced mean arterial pressure and hence a reduced colonic blood flow for a sustained period, may lead to an ischaemia reperfusion injury to the gut. This could precipitate bacterial translocation, endotoxin absorption from the bowel and become a potential trigger of sepsis and septic shock.

A common approach to the perioperative treatment of hypotension and reduced urine output associated with epidural block is i.v. fluid resuscitation. We have demonstrated difficulty in returning colonic blood flow to normal levels with fluid resuscitation alone after a single bolus dose of bupivacaine. In addition, the relative unresponsiveness of the renin–angiotensin system to hypotension and the increase in anti-diuretic hormone after sympathetic block[24] could actually lead to fluid retention and precipitate cardiac failure in susceptible patients, when given excess fluid resuscitation to restore hypotension and improve urine output.

This study was carried out in the operating theatre with a combined general and thoracic epidural anaesthetic. The authors accept that the use of postoperative thoracic epidural analgesia tends to involve lower doses of bupivacaine but postoperative hypotension (systolic <100 mm Hg) can still occur in up to 28% of patients.[25 26] On the basis of the presented data, we postulate that hypotension associated with epidural analgesia should be dealt with promptly (this recommendation is included in the 2001 Report of the National Confidential Enquiry into Perioperative Deaths[27]) and that vasopressor therapy be considered early if there is no improvement with intravenous fluids. Finally, to minimize haemodynamic consequences, epidural block should be confined to the fewest necessary segments avoiding splanchnic innervation (T8–L1) when possible.[22]

Acknowledgements

Statistics: Simon Howell Senior Lecturer in Anaesthetics St James Hospital, University of Leeds. Grant: the Special Trustees of the Bristol Royal Infirmary contributed towards the purchase of the DRT4 laser Doppler and probes.

References

1 Chou CC. Intestinal blood flow regulation. In: Dulbecco R, ed. *Encyclopedia of Human Biology*. San Diego: Academic Press, 1992; 4: 547–56

2 Hogan QH, Stadnicka A, Stekiel TA, *et al.* Effects of epidural and systemic lidocaine on sympathetic activity and mesenteric circulation in rabbits. *Anesthesiology* 1995; **79**: 1250–60

3 Hogan QH, Stekiel TA, Stadnicka A, *et al.* Region of epidural blockade determines sympathetic and mesenteric capacitance effects in rabbits. *Anesthesiology* 1995; **83**: 604–10

4 Arndt J, Hock A, Stanton-Hicks M, *et al.* Peridural anesthesia and the distribution of blood in supine humans. *Anesthesiology* 1985; **63**: 616–23

5 Buggy DJ, Smith G. Epidural anaesthesia and analgesia: better outcome after major surgery ? *BMJ* 1999; **319**: 530–1

6 Johansson K, Ahn H, Lindhagen J, *et al.* Effect of epidural anaesthesia on intestinal blood flow. *Br J Surg* 1988; **75**: 73–6

7 Lundberg J, Lundberg D, Norgren L, *et al.* Intestinal haemodynamics during laparotomy: effects of thoracic epidural anaesthesia and dopamine in humans. *Anesth Analg* 1990; **71**: 9–15

8 Vaisanen O, Parviainen I, Ruokonen E, *et al.* Epidural analgesia with bupivacaine does not improve splanchnic tissue perfusion after aortic reconstruction surgery. *Br J Anaesth* 1998; **81**: 893–8

9 Mallinder PA, Hall JE, Bergin FG, *et al.* A comparison of opiate and epidural alterations in splanchnic blood flow using intraoperative gastric tonometry. *Anaesthesia* 2000; **55**· 659–66

10 Spackman DR, Mcleod DM, Pineas SN, Leach RM, Reynolds F. Effect of epidural blockade on indicators of splanchnic perfusion and gut function in critically ill patients with peritonitis: a randomised comparison of epidural bupivacaine with systemic morphine. *Intensive Care Med* 2000; **26**: 1638–45

11 Shepherd AP, Riedel GL. Continuous measurement of intestinal mucosal blood flow by Laser Doppler velocimetry *Am J Appl Physiol* 1982; **242**: G668–672

12 Kvernebo K, Lunde OC, Stranden E, et *al.* Human gastric circulation evaluated by endoscopic laser Doppler flowmetry. *Scand J Gastroenterol* 1986, **21**: 685–92

13 Lunde OC, Kvernebo K, Larsen S, *et al.* Evaluation of endoscopic laser Doppler flowmetry for measurement of gastric blood flow. Methodological aspects. *Scand J Gastroenterol* 1988; **23**. 1072–8

14 Ahn H, Linhagen J, Lundgren O Measurement of colonic blood flow with Laser Doppler Flowmetry. *Scand J Gastroenterol* 1986; **21**: 871–80

15 Beard JD, Scott DJ, Evans JM, *et al.* Doppler Flow meter for use in theatre. *Ultrasound Med Biol* 1986; **12**: 883–9

16 Beard JD, Scott DJ, Skidmore R, *et al.* Operative assessment of femorodistal bypass grafts using a new Doppler flow meter. *Br J Surg* 1989; **76**: 925–8

17 Singer M, Clarke J, Bennett ED. Continuous hemodynamic monitoring by oesophageal Doppler. *Crit Care Med*, 1989; **17**: 447–52

18 Esperen K, Jensen EW, Rosenborg D, *et al.* Comparison of cardiac output measurement techniques: thermodilution, Doppler, CO_2-rebreathing and the direct Fick method. *Acta Anaesthesiol Scand* 1995; **39**: 245–51

19 Leather HA and Wouters PF. Oesophageal Doppler Monitoring overestimates cardiac output during lumbar epidural anaesthesia *Br J Anaesth* 2001; **86**· 794–7

20 Arndt JO, Hock A, Stanton-Hicks, *et al.* Peridural anesthesia and the distribution of blood in supine humans. *Anesthesiology* 1985; **63**: 616–23

21 Meissner A, Weber TP, Van Aken H, *et al* Limited upper thoracic epidural block and splanchnic perfusion in dogs. *Anesth Analg* 1999; **89**: 1378–81

22 Quinn H, Hogan MD, Thomas A, *et al.* Region of epidural blockade determines sympathetic and mesenteric capacitance effects in rabbits. *Anesthesiology* 1995; **83**: 604–10

23 Sala C, Garcia-Granero E, Molina MJ, *et al.* Effect of epidural anesthesia on colorectal anastomosis. A tonometric assessment *Dis Colon Rectum* 1997; **40**: 958–61

24 Hopf HB, Arand D, Peters J. Sympathetic blockade by thoracic epidural anaesthesia suppresses renin release in response to hypotension, but activates the vasopressin system. *Eur J Anaesthesiol* 1992; **9**: 63–9

25 De Leon-Casasola OA, Parker B, Lema MJ, *et al.* Postoperative epidural bupivacaine-morphine therapy Experience with 4,227 surgical cancer patients. *Anesthesiology* 1994; **81**: 368–75

26 Crawford ME, Moiniche S, Orbaek J, *et al.* Orthostatic hypotension during postoperative continuous thoracic epidural bupivacaine-morphine in patients undergoing abdominal surgery. *Anesth Analg* 1996; **83**: 1028–32

27 *Changing the Way We Operate The 2001 Report of the National Confidential Enquiry into Perioperative Deaths.* NCEPOD 35–43 Lincolns Inn Fields, London WC2A 3PE, UK

British Journal of Anaesthesia 89 (3): 452–8 (2002)

Comparison of intrathecal fentanyl and diamorphine in addition to bupivacaine for Caesarean section under spinal anaesthesia

C. M. Cowan[1]*, J. B. Kendall[2], P. M. Barclay[3] and R. G. Wilkes[3]

[1]Department of Anaesthesia, Wirral Hospitals, Arrowe Park Road, Upton, Wirral CH49 5PE, UK.
[2]Department of Anaesthesia, The Cardiothoracic Centre, Thomas Drive, Liverpool L14 3PE, UK.
[3]Department of Anaesthesia, Liverpool Women's Hospital, Crown Street, Liverpool L8 7SS, UK
**Corresponding author*

Background. Co-administration of small doses of opioids and bupivacaine for spinal anaesthesia reduces intraoperative discomfort and may reduce postoperative analgesic requirements in patients undergoing Caesarean section. Fentanyl and diamorphine are the two most frequently used agents in UK obstetric anaesthetic practice.

Methods. Seventy-five healthy parturients scheduled for elective Caesarean section under spinal anaesthesia using hyperbaric 0.5% bupivacaine, were randomly allocated to additionally receive intrathecal fentanyl 20 μg, diamorphine 300 μg or 0.9% saline. Patients also received i.v. cyclizine and rectal diclofenac.

Results. Less supplementary intraoperative analgesia was required by patients in either opioid group (4%) compared with the control (32%) ($P<0.05$). Twenty four hours after spinal injection, total mean (SD) postoperative morphine requirement was significantly lower if diamorphine was administered (31 (21) mg), in comparison with the other two groups (control 68 (26) mg; fentanyl 62 (26) mg) ($P<0.05$). Reduced visual analogue pain scores were evident 12 h following diamorphine, but observed only for 1 h after fentanyl when compared with the control ($P<0.05$). Mild pruritis was more common for 2 h after either spinal opioid ($P<0.05$), but no inter-group differences were observed for the remainder of the first 24 h. Patients displayed deeper levels of sedation both acutely and 12 h after administration of intrathecal fentanyl ($P<0.05$).

Conclusions. Both intrathecal opioids reduce intraoperative discomfort, but only diamorphine reduced postoperative analgesic requirement beyond the immediate post-operative period.

Br J Anaesth 2002; **89**: 452–8

Keywords: analgesia, postoperative; analgesics opioid, fentanyl; analgesics opioid, diamorphine; surgery, obstetric

Accepted for publication: April 18, 2002

Small doses of opioids administered directly into the cerebrospinal fluid (CSF) have been found to be very effective in controlling symptoms of pain in many clinical situations.[1] This technique has also been used in an attempt to minimize discomfort during and after Caesarean section.[2–4] However, beneficial analgesia has to be balanced against known adverse effects, including respiratory depression, emetogenesis and pruritis. With many opioids currently available, agent and dosage selection are known to influence this risk–benefit balance.[5] Recent work has indicated that intrathecal fentanyl is used by over 40% of UK obstetric anaesthetists; more than twice as frequently as diamorphine.[6] Both have been investigated in attempts to quantify their most effective doses when used for spinal anaesthesia for elective Caesarean section.[7 8] However, there appears to be little information on whether one is more suitable than the other in this situation.

The principal objective of our investigation was to compare the postoperative analgesic properties of fentanyl and diamorphine (in conjunction with bupivacaine), when administered at apparently optimum dosage. In the course of the study, we also examined the intraoperative and potential adverse effects of these intrathecal opioids.

Methods

Prior to commencing the investigation, approval was obtained from both the regional ethical and the hospital

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

research committees. Patients were selected from a cohort scheduled for elective Caesarean section, classified as either ASA I or II, and having no specific contra-indications to receiving non-steroidal anti-inflammatory drugs. Written informed consent was obtained from each, after discussing the study objectives, patient-controlled analgesia (PCA) system and rectal diclofenac administration. Participants were randomly allocated to one of control, fentanyl or diamorphine groups using a sealed envelope technique. Patients were premedicated orally with ranitidine 150 mg the night before and 2 h prior to surgery, in addition to receiving 30 ml of 0.3 M sodium citrate immediately before being escorted to theatre.

With the patient in the sitting position, i.v. access was established using a 16-gauge cannula, and a baseline non-invasive arterial pressure measurement taken. A fluid preload of 2 litres of warmed compound sodium lactate solution was then infused intravenously over approximately 10 min, using a pressurized infusion device. After infiltrating the skin and inter-spinous ligament over the L3/4 interspace with 1% lidocaine 2 ml, the subarachnoid space was entered using a 24-gauge pencil-point spinal needle. Once free flow of CSF had been recognized, the intrathecal (i.t.) anaesthetic solution was injected over 20 s, aspirating CSF at the end of the injection to confirm needle position. All patients received 2.75 ml of hyperbaric 0.5% bupivacaine, in addition to 1 ml of unknown adjuvant, constituting a total volume of 3.75 ml. Patients allocated to the control group had 1 ml of 0.9% saline added to their bupivacaine. Similarly, patients in the fentanyl group had 1 ml of fentanyl 20 μg ml^{-1}, and those in the diamorphine group had 1 ml of diamorphine 300 μg ml^{-1}, added to the bupivacaine.

The intrathecal adjuvant solutions were prepared prior to performing the spinal injection by a separate anaesthetist who had no further involvement with each patient. All were prepared under strict aseptic technique, using 0.9% saline where reconstitution and dilution were required. Once prepared, all were deposited into a sterile transparent bag, which was then sealed and labelled with the trial number. The solution was presented in a 2 ml syringe, 1 ml of which was added to the 2.75 ml of bupivacaine. Thus, the anaesthetist who managed each case was unaware of which solution had been administered.

On completion of the spinal injection, the patient was placed in the supine position, with 15° lateral tilt (right hip uppermost). Arterial pressure was measured by an automatic non-invasive monitor at intervals of 1 min, until it became stable. Arterial pressure was monitored at 5-min intervals thereafter until the completion of surgery. If systolic arterial pressure decreased by 30 mm Hg from baseline (or to an absolute value of 90 mm Hg), or if the patient complained of symptoms indicative of incipient hypotension (e.g. nausea), i.v. ephedrine was administered in increments of 6 mg as required.

The level of anaesthesia was deemed adequate for surgery when loss of cold sensation to ethyl chloride spray was evident from dermatomes L2 to T5. If the patient experienced discomfort during surgery, i.v. alfentanil was administered in 250 μg increments as required for relief. After delivery of the neonate and clamping of the umbilical cord, i.v. syntocinon 10 i.u. was given. An attending paediatrician assessed the neonatal Apgar scores at 1 and 5 min after delivery. According to our usual practice, all patients received i.v. cyclizine 50 mg and diclofenac 100 mg per rectum after the completion of surgery. A urinary catheter was left *in situ* according to our unit policy, to be removed 24 h later.

Immediately following the procedure, patients were transferred to a dedicated recovery ward, and remained there for 1 h. At this point a Graseby 9300 PCA (Watford, Herts, UK) system was attached to a valved Y-connector in the intravenous fluid infusion line, close to the cannula. The PCA was set to deliver a 1 mg bolus of morphine upon demand, with a lock-out time of 3 min and no background infusion. Patients then returned to a six-bedded maternity ward, where they were under constant supervision by a midwife. Anti-emetic (intramuscular (i.m.) cyclizine 50 mg) and anti-pruritic (i.m. chlorpheniramine 10 mg) therapy were also prescribed, to be given every 8 h as required. No other analgesic medication was prescribed for the first 24 h following the spinal injection. After this time, the PCA device could be substituted for analgesics in the form of acetaminophen 1 g and codeine phosphate 8 mg orally 6 hourly, and diclofenac 100 mg per rectum 16 hourly, as required.

Formal assessment of the patients was conducted at 1, 2, 6, 12, and 24 h after the spinal injection. Pain was recorded on a 0–100 mm visual analogue scale (VAS) using a ruler device donated by Napp Pharmaceuticals Ltd. (Cambridge, Cambridgeshire, UK). Nausea and pruritis were assessed on a modified four point ordinal scale.[9] Level of sedation was assessed using another four point ordinal scale. Both scoring systems are outlined in Table 1.

Data analysis

After discontinuation of the PCA system, the Graseby 9300 device was interrogated by a link to a desktop computer using Hyperterminal® (Hilgraeve Inc., Monroe, Michigan, USA) supported by Microsoft™ Windows '98, in order to obtain the hourly morphine consumption data. Based upon previous work,[3] a sample size of 25 patients per group was estimated to detect an inter-group difference of morphine 20 mg requirement 24 h after intrathecal injection (α=0.05, β=0.8). Statistical tests were performed using SPSS™ v9.0 and Graphpad Instat™ v3.05 for Microsoft™ Windows '98, and results are reported as absolute values, mean (SD or 95% confidence intervals), or *median* [inter-quartile range] or {range} where appropriate. At selected times after surgery, the morphine consumption and VAS pain scores of the three groups were compared using analysis of variance (with Bonferroni post-hoc analysis). Intraoperative ephedrine and

Table 1 Ordinal scales used to assess severity of nausea, pruritis and level of sedation

Score	Nausea and pruritis assessment
0	no symptoms
1	mild symptoms, but not requesting treatment
2	moderate symptoms, requesting treatment
3	symptoms persisting despite treatment
Score	**Sedation assessment**
0	awake and alert
1	drowsy, but responds to verbal stimulus
2	drowsy, but responds to physical stimulus
3	unresponsive

Table 2 Patient characteristics expressed as mean (SD) and proportions

Characteristic	Control	Fentanyl	Diamorphine
Age (yr)	31.5 (4.6)	32.6 (5.0)	30.3 (5.4)
Body mass index (kg m^{-2})	27.4 (3.3)	27.9 (3.6)	27.5 (2.9)
Gestation (weeks)	38.1 (0.6)	38.0 (0.7)	37.9 (0.9)
Previous Caesarean section (yes)	68%	52%	76%

Table 3 Intraoperative pain, ephedrine requirements, duration of surgery and neonatal Apgar scores, classified according to intrathecal group. Results are expressed as absolute numbers (%), *median* [inter-quartile range] or {range}. $^{§}P<0.05$ *vs* fentanyl, $^{†}P<0.05$ *vs* diamorphine

Observation	Control	Fentanyl	Diamorphine
Intraoperative pain (*n* (%))	8 (32)$^{† §}$	1 (4)	1 (4)
Ephedrine dose (mg)	*12* [6–27]	*12* [0–25]	*9* [0–22]
Spinal injection to end of surgery time (min)	*49* {30–56}	*47* {30–50}	*42* {25–54}
Apgar @ 1 min (score)	*9* {8–9}	*9* {6–10}	*9* {6–10}
Apgar @ 5 min (score)	*10* {9–10}	*10* {9–10}	*10* {9–10}

Table 4 Summary of postoperative morphine requirements, classified according to intrathecal adjuvant. Results are expressed as mean (standard deviation) $^{§}P<0.05$ *vs* fentanyl, $^{†}P<0.05$ *vs* diamorphine

Time (h)	Control (mg)	Fentanyl (mg)	Diamorphine (mg)
2	8.3 (9.3)†§	3.1 (3.7)	2.9 (2.8)
6	28.5 (12.7)†	24.0 (12.6)†	12.5 (10.4)
12	42.4 (18.3)†	38.2 (18.5)†	17.7 (12.4)
24	68.4 (26.6)†	61.6 (25.5)†	31.3 (21.2)

alfentanil requirements, neonatal Apgar scores, and postoperative patient nausea, pruritis and sedation scores were analysed by a Kruskal–Wallis test (with Dunn's post-hoc test). Categorical data were examined using χ^2 analysis. A P value of less than 0.05 was considered statistically significant.

Results

Full data collection was achieved for all of the 75 patients that participated in the investigation. There were no differences with regard to patient age, body mass index, or duration of gestation between the three groups. In addition, there was no significant inter-group difference in terms of patients having undergone a previous Caesarean section (Table 2).

Intraoperative analgesic supplementation was required in significantly more of the patients belonging to the control group (8/25; 32%) compared with either of the opioid groups (both 1/25; 4%) (Table 3). However, there were no differences in total amounts of ephedrine required to maintain normotension during the procedure (median values: control, 12 mg; fentanyl, 12 mg; diamorphine, 9 mg). Similarly, the neonatal Apgar scores after 1 and 5 min were no different between groups (median values at 5 min: control, 10; fentanyl, 10; diamorphine, 10), although when assessed after 1 min, four neonates from the fentanyl group and one from diamorphine group had a score of less than 7.

Morphine consumption from the PCA device was examined on a cumulative and hourly basis (Table 4). When 24 h had elapsed after intrathecal injection, patients who received i.t. diamorphine had used significantly less morphine than those in the control and fentanyl groups (mean values: control, 68 mg; fentanyl, 62 mg; diamorphine, 31 mg). Cumulative morphine consumption of patients who received fentanyl was significantly lower than those in the control group until 4 h, but thereafter no significant difference was observed.

Hourly morphine consumption is represented by the 2-h moving average and is illustrated in Figure 1. Patients in the fentanyl group used less analgesia than those in the control group for the first 3 h, but thereafter their hourly requirements were no different. In contrast, those who received diamorphine used less hourly morphine than the controls until 19 h after spinal injection, with no difference thereafter. Patients who received fentanyl used significantly more hourly morphine than those who received diamorphine from 4 until 20 h following the spinal injection. An exception exists between 13 and 16 h when no inter-group difference was evident. One hour following spinal injection, patients who received either spinal opioid complained of significantly less pain (Fig. 2), but by 2 h only those that received diamorphine were in less pain than those in the control group. No difference in pain scores was evident when examined at 6 and 24 h, but when assessed after 12 h, patients in the control group were in significantly more discomfort than those in the diamorphine group.

There were no recorded episodes of respiratory depression (respiratory rate of less than 10 bpm) in any of the patients. In addition, there were no significant differences between patient groups in terms of respiratory rate throughout the 24-h observational period. Other adverse effects (sedation, pruritis, and nausea) were graded according to an ordinal scoring system (Table 1). Sedation appeared to be

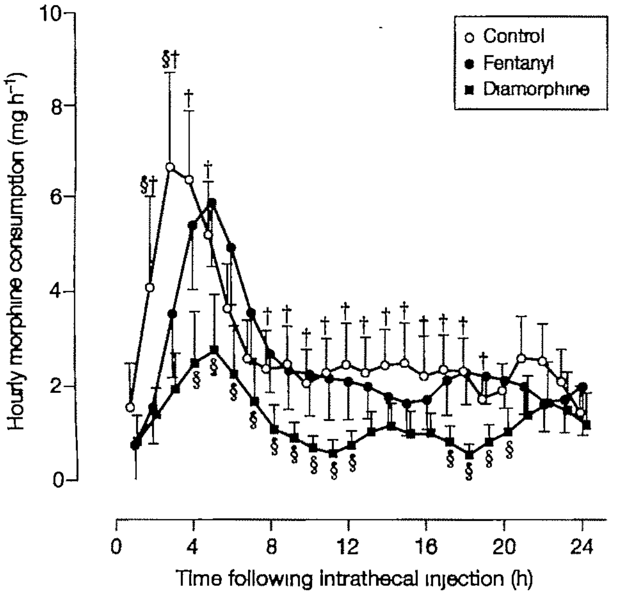


Fig 1 Hourly morphine consumption in the 24 h following intrathecal injection subclassified by patient group. $^{\S}P<0.05$ *vs* fentanyl; $^{\dagger}P<0.05$ *vs* diamorphine

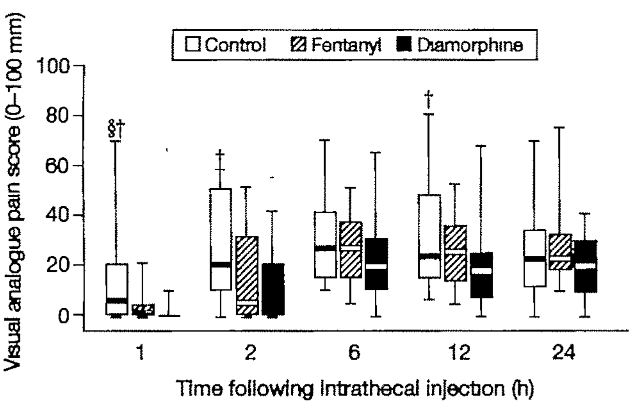


Fig 2 Visual analogue pain scores (0–100 mm) in the 24 h following intrathecal injection, subclassified according patient group (central bar, median; box area, inter-quartile range; whiskers, range) $^{\S}P<0.05$ *vs* fentanyl, $^{\dagger}P<0.05$ *vs* diamorphine.

more likely to occur in those patients who received fentanyl (Table 5). One hour after spinal injection, these patients exhibited a significantly greater degree of sedation than those in the control group. Additionally, when assessed after 12 h, these patients appeared significantly more drowsy than patients in both control and diamorphine groups. One hour after spinal injection, the problem of itching was no different between patient groups, but by 2 h, those who had received either opioid were significantly more itchy than those who had not (Table 5). However, in only one of these patients was itching severe enough to require anti-pruritic treatment. From 6 h onwards, there were no differences in pruritis levels between any of the patient groups. Nausea and vomiting occurred relatively infrequently (Table 5), with no differences observed between the patient groups. The highest incidence was observed in those patients who received fentanyl (24%), 12 h after spinal injection.

Discussion

This study demonstrated that patients undergoing Caesarean section under spinal anaesthesia experienced less discomfort during the procedure when either fentanyl or diamorphine were added to the intrathecal injectate. However, only the addition of diamorphine significantly reduced the need for further analgesia after surgery.

Patients undergoing Caesarean section under spinal anaestheisa may benefit from the co-administration of local anaethetic and opioid agents, because of improved intraoperative comfort,[10] apparent prolongation of spinal analgesic action,[7] and reductions in postoperative requirements for additional analgesia.[11] However, these advantages need to be balanced against problems such as pruritis, nausea, sedation and respiratory depression. Fentanyl and diamorphine are the two most frequently used spinal opioids by obstetric anaesthetists in the UK,[6] for several reasons. Both are readily available commercially in a preservative free formulation. Both have sufficient lipid solubility[12] to enable rapid penetration of neuronal tissue, hindering cephalad migration induced by CSF currents,[1] the probable cause of side-effects.[13 14] Diamorphine undergoes metabolism within spinal cord tissue generating active compounds (6-acetyl morphine and morphine). These metabolites are less lipid soluble than the parent drug, and limit their back-diffusion into the CSF.[15] Both fentanyl and diamorphine have been investigated for use in Caesarean section by dose-finding studies.

Fentanyl has been investigated on a dose per kilogram body weight basis in a study where the average patient weight was 80 kg,[16] which approximated to examining effects following doses of 20, 40 and 60 µg. Intraoperative respiratory depression and increased sedation was observed in those that received 40 µg or more. A further study[7] considered a larger number of possible doses, and showed that even a dose of 6.25 µg was sufficient to prolong spinal analgesic action. Patients who received doses of 12.5 and 25 µg displayed a trend toward lower postoperative analgesic requirements, but did not reach statistical significance. However, patients who received doses of 25 µg (or more) experienced troublesome pruritis. Other workers studied the effects following doses of 15 µg[3] and 25 µg,[17] the latter identifying late-onset increases in postoperative analgesic requirements. These studies seem to indicate that in order to maximize postoperative analgesia, whilst minimizing respiratory depression and pruritis, a dose of 20 µg would appear to be optimal.

Intrathecal administration of diamorphine has also been the subject of dosage analysis. An earlier investigation[4]

Table 5 Postoperative nausea, pruritus and sedation scores (expressed as numbers of patients), in the first 24 h after spinal injection, classified according to intrathecal adjuvant. [‡]$P<0.05$ *vs* fentanyl, [†]$P<0.05$ *vs* diamorphine

Time (h)	Group	Nausea score				Pruritis score				Sedation score			
		0	1	2	3	0	1	2	3	0	1	2	3
1	Control	24	1	–	–	20	4	1	–	24[‡]	1[‡]	–	–
	Fentanyl	23	2	–	–	23	–	2	–	18	6	1	–
	Diamorphine	25	–	–	–	24	1	–	–	22	3	–	–
2	Control	24	1	–	–	23[‡†]	2[‡†]	–	–	23	–	2	–
	Fentanyl	23	2	–	–	11	14	–	–	23	2	–	–
	Diamorphine	23	2	–	–	12	12	1	–	25	–	–	–
6	Control	22	2	–	1	19	6	–	–	23	2	–	–
	Fentanyl	20	3	1	1	18	7	–	–	18	7	–	–
	Diamorphine	23	1	1	–	17	8	–	–	23	2	–	–
12	Control	20	3	–	2	18	7	–	–	24[‡]	1[‡]	–	–
	Fentanyl	19	5	–	1	19	6	–	–	18	7	–	–
	Diamorphine	22	3	–	–	19	6	–	–	24[‡]	1[‡]	–	–
24	Control	23	2	–	–	20	4	1	–	25	–	–	–
	Fentanyl	20	4	–	1	21	4	–	–	22	3	–	–
	Diamorphine	23	2	–	–	24	1	–	–	25	–	–	–

administered doses in 125 μg increments, and found significantly lower postoperative analgesic consumption in patients given 250 or 375 μg, but that the latter group experienced excessive degrees of vomiting and pruritis. A similar study[8] reported lowest analgesic requirements in patients receiving 300 μg, and since this dose did not appear to provoke excessive degrees of pruritis or nausea, it was chosen as the optimum dose of diamorphine.

A systematic review of intraoperative analgesia[10] identified that approximately 24% of patients that receive only hyperbaric bupivacaine experience unacceptable levels of discomfort during spinal anaesthesia for Caesarean section. The addition of most opioids to the spinal injectate attenuate this effect.[8,16] Our investigation found that only 4% (one patient) in either opioid group needed additional analgesia intraoperatively, in contrast to 32% of patients in the control cohort. The number of patients needed to treat with either spinal opioid in order to prevent one patient feeling excessive discomfort is 3.6, indicating a high degree of clinical effectiveness.

When attempting to quantify postoperative analgesic requirements, observation of consumption from a PCA system remains the method least likely to be affected by bias.[18] Cumulative morphine consumption, beyond the immediate postoperative period, was significantly lower only in those patients who received diamorphine, when compared with those in either the control or fentanyl groups. Previous studies recognized that diamorphine does possess analgesic sparing qualities,[4,8] whilst the findings of others reflect uncertainty over fentanyl's capacity for similar effects.[3,7,16,17] This investigation finds that intrathecal fentanyl does not appear to reduce cumulative analgesic requirements past the point of 4 h.

Analysing the hourly morphine consumption provided additional insight into this finding. Patients in the fentanyl group appear to begin loading themselves with morphine 3 h after spinal injection, only 1 h later than those in the control group. The existence of this extra 'golden hour' of analgesia had been noted by previous workers.[3,9] Beyond this 3-h point, the patients in the fentanyl and control groups have no discernible differences in their analgesic requirements. On this evidence, i.t. fentanyl appears to have no long acting analgesic properties. Patients who received diamorphine seem to have a biphasic nature to their analgesic consumption, with one noticeable peak after 5 h, and a second after 20 h, when the requirements of the three groups converge. This represents a significantly lower hourly morphine requirement compared to both the control and the fentanyl groups, and appears to last for up to 19 h following intrathecal administration.

Using a PCA system allows patients to self medicate until they find an individually acceptable level of comfort. Hence, one might not expect to observe any differences in terms of pain experiences. However, the patients' pain scores also reflect the above pattern of analgesic efficacy, with those who received either opioid in significantly less discomfort when interviewed 1 h after the spinal injection. When interviewed after 2 h, those in the fentanyl group had similar levels of discomfort to those in the control, whilst those in the diamorphine group still complain of less pain. There appears to be no difference between the three groups when questioned after 6 and 24 h, a finding which has been also reported in earlier work.[8] However, the observation after 12 h indicates that the diamorphine group were in significantly less discomfort than the controls. This suggests that this may also have been the case after 6 h, had this study been powered on the basis of pain scores.

Although opioids confer improved intraoperative (and in the case of diamorphine, postoperative) analgesia profiles, concern remains that these may be tempered by an increased incidence of adverse effects.

Respiratory depression is associated with the use of intrathecal narcotics,[19] and analysis of arterial carbon dioxide tension has demonstrated its presence despite a normal respiratory frequency.[20] However, the observation of a lucid patient, breathing at an acceptable rate, currently remains the most clinically applicable method of safeguarding patients from this complication.[5] Previous work has demonstrated that patients undergoing Caesarean section exhibit a degree of resistance to the respiratory depressant effects of intrathecal opioid.[21] This study found that the use of either spinal opioid was not associated with a decreased respiratory rate, in agreement with previous studies.[3 4 7 22]

Acute onset sedation has been previously described in association with i.t. fentanyl,[18] and a non-significant trend toward late onset sedation has also been observed.[17] An increased propensity to develop sedation was observed in those patients who received fentanyl, this being statistically significant when observed after 1 and 12 h (Table 5). Interestingly, it is after 12 h have elapsed that these patients' use of the PCA device declined slightly (Fig. 2), and may be because they are becoming somnolent. In contrast, patients belonging to the control or diamorphine groups did not appear to develop excessive sedation. This is in keeping with a previous study,[22] with similar findings following 250 μg of i.t. diamorphine.

Itching can be a distressing side effect, which is associated with systemic opioid administration, particularly when given neuraxially. Incidence can be as high as 80%,[22] but symptoms are generally mild in nature. The use of non-steroidal anti-inflammatory drugs in the analgesic strategy has been noted to reduce pruritis in a general surgical setting.[23] However, incidence of itching after spinal opioids in patients following Caesarean section remains high despite this intervention.[8] We found itching was present in significantly more patients 2 h after administration of either spinal opioid (approximately 55%), but in only one of these patients was it severe enough to require anti-pruritic therapy. From 6 h onwards the prevalence was no different between the three groups (approximately 25%), displaying the potential for i.v. morphine to also induce this side effect. The fact that our highest incidence (55%) was marginally lower than other studies,[22] may be attributable to the use of cyclizine as a prophylactic anti-emetic in all our patients, which has anti-histaminic (H_1) properties.

Spinal opioid use can exacerbate postoperative nausea and vomiting, particularly when used at higher dose regimens.[4] This side effect can also be agent specific, with morphine more likely to induce it than diamorphine.[2] Reported incidences vary from 25% following 12.5 μg i.t. fentanyl,[7] to 70% following 300 μg i.t. diamorphine.[8] This investigation identified no significant differences between any of the groups. The incidence was relatively low, ranging from less than 10% in the 2 h immediately postoperatively, to approximately 20% after 12 h. Prophylactic anti-emetic therapy may have helped to limit nausea, especially in the first 5 h after surgery, a strategy not employed in other studies.[7 8]

This study found that low doses of either spinal opioid had no adverse impact on neonatal condition, when determined by Apgar scoring, which is in concordance with other investigations.[3 4 7 16]

In conclusion, we found that the inclusion of fentanyl or diamorphine in the subarachnoid injectate enhances intraoperative comfort during Caesarean section, with no undesirable effects on haemodynamic stability or neonatal condition. However, i.t. fentanyl appears to provide only 1 h of additional analgesia over hyperbaric bupivacaine alone, has no long acting analgesic sparing effect, but can predispose to greater depth of sedation. When administered in conjunction with i.v. cyclizine and rectal diclofenac, i.t. diamorphine results in significantly lower analgesic requirements for up to 19 h after surgery, whilst appearing not to cause excessive problems of sedation, itching or nausea. Presently, only 20% of obstetric anaesthetists in the UK add diamorphine to intrathecal bupivacaine, the majority preferring fentanyl or no opioid.[6] In the light of our findings, we suggest that this practice should be reviewed.

References

1 Cousins MJ, Mather LE. Intrathecal and epidural administration of opioids. *Anesthesiology* 1984; **61**: 276–310

2 Roulson C, Chan A, Albin M, Carli F. Intrathecal morphine or diamorphine for cesarean section? Preliminary findings. *Int J Obstet Anesth* 1994; **3**: 173

3 Shende D, Cooper GM, Bowden MI. The influence of intrathecal fentanyl on the characteristics of subarachnoid block for caesarean section. *Anaesthesia* 1998; **53**: 702–10

4 Kelly MC, Carabine UA, Mirakhur RK. Intrathecal diamorphine for analgesia after caesarean section. *Anaesthesia* 1998; **53**: 231–7

5 Etches RC Sandler AN, Daley MD. Respiratory depression and spinal opioids. *Can J Anaes* 1989; **36**· 165–85

6 Burns SM, Cowan CM, Wilkes RG. Prevention and management of hypotension during spinal anaesthesia for elective Caesarean section: a survey of practice. *Anaesthesia* 2001; **56**: 794–8

7 Hunt CO, Naulty JS, Bader AM. Perioperative analgesia with subarachnoid fentanyl-bupivacaine for cesarean delivery. *Anesthesiology* 1989; **71**: 535–40

8 Skilton RWH, Kinsella SM, Smith A, Thomas TA. Dose response study of subarachnoid diamorphine for analgesia after elective caesarean section. *Int J Obstet Anesth* 1999; **8**: 231–5

9 Dahlgren G, Hulstrand C, Jakobsson J, Norman M, Eriksson EW, Martin H. Intrathecal sufentanil, fentanyl, or placebo added to bupivacaine for cesarean section. *Anesth Analg* 1997; **85**: 1288–93

10 Dahl JB, Jeppesen IS, Jørgensen H, Wetterslev J, Møiniche S. Intraoperative and postoperative analgesic efficacy and adverse effects of intrathecal opioids in patients undergoing cesarean section with spinal anaesthesia. *Anesthesiology* 1999; **91**: 1919–27

11 Graham D, Russell I. Double blind study to assess the analgesic sparing effect of 0.3 mg diamorphine given intrathecally at caesarean section. *Int J Obs Anesth* 1995; **4**: 178–89

12 Bullingham RES, McQuay HJ, Moore RA. Extradural and intrathecal narcotics. *Recent Adv Anesth Analg* 1982, **14**: 141–56

13 Florez J, McCarty LE, Borison HL. A comparative study in the cat

of the respiratory effects of morphine injected intravenously and into the cerebrospinal fluid. *J Pharmacol Exp Ther* 1968; **163**: 448–55

14 Bromage PR, Camporesi EM, Durant PAC, Nielsen CH. Non-respiratory side effects of epidural morphine. *Anesth Analg* 1982; **61**: 490–5

15 Stevens LA, Wootton CM. The pharmacokinetic properties of diamorphine. In: Scot DB, ed. *Diamorphine. Its Chemistry, Pharmacology and Clinical Use.* New York: Woodhead Faulkner, 1988; 15–43

16 Belzarena SD. Clinical effects of intrathecally administered fentanyl in patients undergoing cesarean section. *Anesth Analg* 1992; **74**: 653–7

17 Cooper DW, Lindsay SL, Ryall DM, Kokri MS, Eldabe SS, Lear GA Does intrathecal fentanyl produce acute cross-tolerance to i.v. morphine. *Br J Anaesth* 1997; **78**: 311–3

18 Husaini SW, Russell IF. Intrathecal diamorphine compared with morphine for postoperative analgesia after Caesarean section under spinal anaesthesia. *Br J Anaesth* 1998; **81**: 135–9

19 Gustafsson LL, Schildt B, Jacobsen K. Adverse effects of extradural and intrathecal opiates: report of a nationwide report in Sweden. *Br J Anaesth* 1982; **54**: 479–86

20 Allen PD, Walman T, Concepcion M, Sheskey M, Patterson MK, Cullen D, Covino BG. Epidural morphine provides postoperative pain relief in peripheral vascular and orthopaedic surgical patients· a dose response study. *Anesth Analg* 1986; **65**: 165–70

21 Abboud TK, Dror A, Mosaad P, Zhu J, Mantilla M, Swart F, Gangolly J, Silao P, Makar A, Moore J. Minidose intrathecal morphine for the relief of post-cesarean section pain: safety, efficacy, and ventilatory responses to carbon dioxide. *Anesth Analg* 1988; **67**: 137–43

22 Hallworth SP, Fernando R, Bell R, MG Parry, Lim GH. Comparison of intrathecal and epidural diamorphine for elective Caesarean section using a combined spinal-epidural technique. *Br J Anaesth* 1999; **82**: 228–32

23 Colbert S, O'Hanlon DM, Galvin S, Chambers F, Moriarty DC. The effect of rectal diclofenac on pruritus in patients receiving intrathecal morphine. *Anaesthesia* 1999; **54**: 948–52

British Journal of Anaesthesia 89 (3) 459–65 (2002)

Patient-controlled epidural analgesia *versus* continuous infusion for labour analgesia: a meta-analysis

M. van der Vyver[1], S. Halpern[2*] and G. Joseph[2]

[1]Department of Anaesthesia, University of Stellenbosch and Tygerberg Academic Hospital Private Bag 3, Tygervallei 7505, Western Cape, South Africa. [2]Department of Anaesthesia, University of Toronto and Sunnybrook and Women's Health Sciences Centre, Women's College Campus, 76 Grenville Street, Toronto, Ontario, M5S 1B2 Canada

**Corresponding author*

Background. Patient-controlled epidural analgesia (PCEA) is a relatively new method of maintaining labour analgesia. There have been many studies performed that have compared the efficacy of PCEA with continuous epidural infusion (CEI). The purpose of this systematic review is to compare the efficacy and safety of PCEA and CEI.

Methods. All randomized controlled trials that compared PCEA, without background infusion, with CEI were sought from the literature. These were rated for quality using a validated, five-point scale. The primary outcome was the number of patients who received anaesthetic interventions. Secondary outcomes included the dose of local anaesthetic, incidence of motor block, quality of analgesia, obstetric and safety outcomes. Where feasible, the data were combined using meta-analytical techniques. For dichotomous data, the risk difference (RD) and 95% confidence intervals (CI) were calculated. For continuous data, the weighted mean differences (WMD) were calculated. The differences were statistically significant when the 95% CI excluded 0.

Results. Nine studies comprised of 640 patients were found. There were fewer anaesthetic interventions in the PCEA group (RD, 27%; 95% CI, 18–36%; $P<0.00001$). This group also received less local anaesthetic (WMD, –3.92; 95% CI, –5.38 to –2.42; $P<00001$) and less motor block (RD, 18%; 95% CI, 6–31%; $P=0.003$). Both methods were safe for mother and newborn.

Conclusion. Patients who receive PCEA are less likely to require anaesthetic interventions, require lower doses of local anaesthetic and have less motor block than those who receive CEI. Future research should be directed at determining differences in maternal satisfaction and obstetric outcome.

Br J Anaesth 2002; **89**: 459–65

Keywords: analgesia, obstetric; analgesia, patient-controlled; analgesic techniques, epidural; safety, techniques

Accepted for publication: April 11, 2002

Epidural analgesia is the most effective way of providing pain relief in labour.[1] A number of techniques have evolved to maintain the level of analgesia throughout labour. Historically, intermittent bolus dosing of local anaesthetic by the clinician (anaesthetist, nurse or midwife) was used. However, this technique had a number of drawbacks including inconsistent analgesia, potential toxicity, and concerns about sterility each time the clinician opened the system to administer a bolus.

Continuous epidural infusion (CEI) of local anaesthetics was introduced into common clinical practice in the 1980s. While the technique has circumvented a number of difficulties,[2] it is not ideal. Many patients still required clinician-initiated top-ups and experienced unacceptably dense motor block in the lower extremities. Although many combinations of infusion rates and various concentrations of local anaesthetics and additives have been investigated, these problems persist.

Patient-controlled epidural analgesia (PCEA) for relief of labour pain was first described by Gambling in 1988 [3] This technique allowed the patient to control the dose of epidural medication as labour and pain patterns changed. It also

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Table 1 PCEA *vs* CEI study characteristics. B=bupivacaine, R=ropivacaine, epi=epinephrine, F=fentanyl; S=sufentanil, PCEA=patient-controlled epidural analgesia; CEI=continuous epidural infusion; UA=umbilical artery, UV=umbilical vein

Reference number (year)	Quality score	Patients (*n* PCEA/ *n* CEI)	PCEA group treatment	CEI group treatment	Population	Outcomes measured	Significantly different outcomes
16 (2001)	5	27/29	0.1% R, F 2 μg ml^{-1}; bolus 5 ml, lockout 10 min, max 25 ml h^{-1}	0.1% R; F 2 μg ml^{-1}, 8 ml h^{-1}	Nulliparous	R/F ml h^{-1}, midwife top-ups, VAS every 15–30 min, motor weakness (ambulation), obstetric outcomes, hypotension and 1 and 5 min Apgar scores	None
11 (1994)	4	30/30	0.125% B, bolus 6 ml; lockout 20 min; no max	0.125% B, 10 ml h^{-1}	Mixed parity	Analgesia, patient satisfaction, motor block, sensory level, B mg h^{-1}, number of top-ups, duration of labour, mode of delivery and hypotension.	Mean B mg h^{-1}, patient satisfaction and number of top-ups: favouring PCEA
14 (1993)	4	55/13	0.125% B, F 2.5 μg ml^{-1}, E 1 400000; bolus 2–6 ml, lockout 10–30 min	0.125% B, F 2.5 μg ml^{-1}, E 1 400000 8 ml h^{-1}	Nulliparous	Analgesia, patient satisfaction, motor block, numbers of patients requiring clinician-interventions. mean B mg h^{-1} and F μg h^{-1}, mode of delivery, hypotension and Apgar scores	Mean B mg h^{-1} and F μg h^{-1}, and spontaneous deliveries· all favouring PCEA
12 (1991)	3	20/20	0.125% B, F 2 μg ml^{-1}; bolus 3 ml; lockout 10 min; no max	0.125% B, F 2 μg ml^{-1}; 12 ml h^{-1}	Mixed parity	Analgesia, motor block, sensory level, B mg h^{-1}, F μg h^{-1}, number of clinician top-ups, duration of labour (1st and 2nd stage), mode of delivery, hypotension, pruritus and Apgar scores	Hourly B mg h^{-1} ($P<0.0002$) and F μg h^{-1} ($P<0.0002$): lower in PCEA.
13 (1994)	3	15/15	0.125% B, F 2 μg ml^{-1}; bolus 3 ml; lockout 10 min, no max	0.125% B, F 2 μg ml^{-1}, 12 ml h^{-1}	Mixed parity	Analgesia, motor block, sensory level, B mg h^{-1}. number of clinician top-ups, duration of labour (1st and 2nd stage), mode of delivery, hypotension and Apgar scores.	B mg h^{-1} less in treatment group ($P<0.0002$); number of spontaneous vaginal deliveries less in CEI ($P<0.04$)
9 (1999)	2	48/50	0.125% B, S 0.5 μg ml^{-1}, bolus 5 ml; lockout 10 min; max 50 ml 4h^{-1}	0.125% B; S 0.5 μg ml^{-1} at 8–14 ml h^{-1}	Mixed parity	Analgesia, patient satisfaction, motor block, sensory level, total and hourly dose of B. number of patients, requiring clinician top-ups, total duration of labour, mode of delivery, hypotension, pruritus and Apgar scores	B mg h^{-1} less in PCEA ($P<0.05$), smaller number of patients requiring top-ups in treatment group ($P<0.05$).
10 (1999)	1	44/46	0.1% B, F 2 μg ml^{-1}; bolus 10 ml, lockout 30 min; no max	0.1% B; F 2 μg ml^{-1}; 10 ml h^{-1}.	Nulliparous	Analgesia, patient satisfaction, motor block, B mg h^{-1}, F μg h^{-1}, number of patients. requiring top-ups, total duration of labour, mode of delivery, Apgar scores >UA and UV pH	Motor and block, B dose h^{-1}. in favour of PCEA.
7 (1992)	1	75/84	0.25% B; bolus 3 ml; lockout 5 min, max 4 boluses h^{-1}	0.125% B 10 ml h^{-1}	Nulliparous	Analgesia, patient satisfaction, motor block, mean total B mg, number of anaesthetist interventions, duration of second stage, mode of delivery and hypotension	Motor block less in PCEA group ($P<0.01$); number of anaesthetist interventions less in PCEA groups.
8 (1994)							
15 (1999)	1	20/20	0.2% R; bolus 5 ml; lockout 15 min; max 15 ml h^{-1}	0.2% R 8 ml h^{-1}	Nulliparous	Analgesia, motor block, sensory level, R mg h^{-1}, number of clinician top-ups, duration of second stage, mode of delivery, hypotension, shivering, nausea and Apgar scores	R mg h^{-1} dose lower in PCEA group ($P<0.05$), motor block less in PCEA group ($P<0.05$).

allowed for individualization of drug dosage by the patient, allowing her to trade off therapeutic effects (e.g. complete pain relief) and side-effects (e.g. motor block). However, the equipment needed for PCEA may be more expensive than CEI. Also, more time is required to educate both the patient and staff about the appropriate use of the medication and equipment.

Many studies have been performed comparing PCEA with CEI. The purpose of this systematic review is to compare the efficacy and safety of PCEA with that of CEI for maintenance of labour analgesia.

Methods

We sought randomized controlled trials (RCTs) that compared PCEA with CEI. Reports were identified by electronically searching Medline (January 1980 to September 2001), EMBase (January 1980 to September 2001), Science

Citation index (1993–2001) and the Cochrane Library (June 2000, Issue 3).

We used the following search terms as key words and text words: 'Patient-controlled', 'labour analgesia', 'anaesthesia' (excluding anaesthesia for Caesarean section) and 'pregnancy'. Alternative spellings of the search terms were also used. No language restriction was applied. The last search was done on the September 20, 2001. Additional reports were identified from reference lists of retrieved reports and review articles.

We included published RCTs in healthy parturients that used the same local anaesthetic and additives for both the study and control group. Furthermore, we only included RCTs that had no continuous background infusion in the PCEA group. We excluded abstracts of scientific meetings, unpublished observations and correspondence.

Each report meeting the inclusion criteria, was read independently by each of the authors and assigned a quality score according to a previously published, validated scale.[4] This scale consists of three items and has a maximum possible score of five. When the report was described as randomized, one point was given. If the randomization process was appropriate an extra point was given. The original point for randomization was lost if randomization was inappropriate (e.g. if it was based on date of birth). One point was given when a study was described as blinded. If blinding was inappropriate this point was lost, but an extra point was gained if blinding was appropriate. If all patients randomized were fully accounted for another point was given. The final quality score for each article was reached by the authors by means of consensus.

The primary outcome of the study was the number of patients who received anaesthetic interventions during the maintenance of labour analgesia. Secondary outcomes included the dose of local anaesthetic, the incidence of motor block, the quality of analgesia and maternal satisfaction. Obstetric and neonatal outcomes included the length of labour, rate of Caesarean section, the rate of instrumental deliveries and the incidence of low Apgar scores at 1 and 5 min. Other outcomes included the incidence of hypotension, high block, nausea, pruritus and shivering.

Data were recorded independently by two of the authors (M.V. and G.J.) and discrepancies resolved by reinspection of the original articles. The data were entered into the statistical program (S.H.H) and rechecked (M.V.).

Where feasible, meta-analytical techniques, using a random effects model were used (Metaview software, Revman 4.1, Cochrane Library, Oxford, UK). For dichotomous data, the risk difference (RD) and 95% confidence intervals (95% CI) were calculated. For continuous data, the weighted mean difference and 95% CI were calculated. We considered the results statistically significant if the 95% CI excluded 0. The χ^2 test was used to calculate heterogeneity and a P-value of <0.05 was regarded as significant. Where meta-analysis was not appropriate, the results of the individual studies were reported. We also performed a sensitivity analysis on the primary outcome on the basis of the quality score (0–2 *vs* 3 or more).

Results

We identified a total of 12 RCTs. Two manuscripts were not available through the University of Toronto Library system and were excluded.[5 6] The outcome of one of the studies was reported in two manuscripts.[7 8] Therefore, nine studies (in ten manuscripts) described a total of 641 patients of whom 545 patients received bupivacaine[7–14] and 96 patients received ropivacaine.[15 16] The range of numbers of patients included in the studies was 30–159. The median quality score was 3. Five studies had quality scores of three or greater.[11–14 16]

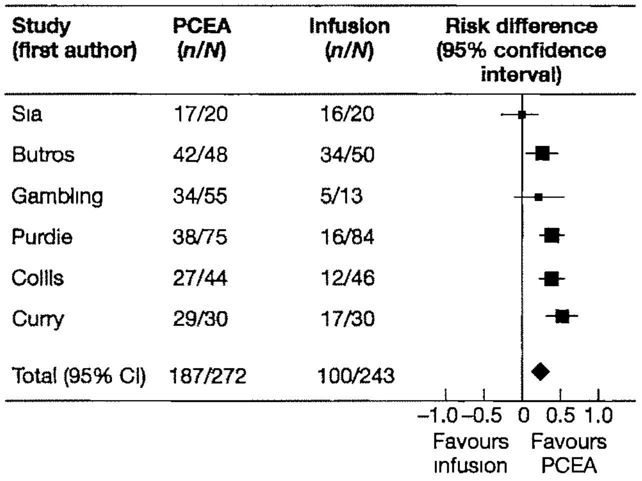
Table 1 details the quality score, the obstetric population studied, the number of patients involved in each group and drugs used for maintenance in PCEA and CEI groups. None of the studies reported the incidence of induced and spontaneous labour. All measured outcomes, as well as those that were significantly different, are shown.

Unscheduled anaesthetic interventions

In five of the studies, clinician top-up of the epidural for inadequate analgesia was reported as a separate outcome.[9–11 14] In one study, this outcome and catheter manipulation or replacement were considered together.[7] Figure 1 shows the combined data for the number of patients who needed no unscheduled anaesthetic interventions. Significantly fewer patients needed clinician top-ups in the PCEA group compared with CEI (RD, 27%; 95% CI, 18–36%; $P<0.00001$). This observation was also true when only studies with a quality score of three or greater were considered (RD, 35%; 95% CI, 19–51%; $P<0.0001$). Although four of the studies included patients of mixed parity,[9 11–13] there was no evidence of heterogeneity ($P=0.36$) among the studies for this outcome.

Three studies reported the number of anaesthetic interventions in a manner that could not be combined in the meta-analysis above. One did not report the number of top-ups but noted the volume of local anaesthetic given per hour. In this study, the midwives administered less ropivacaine in the PCEA group compared with the CEI (5.4 *vs* 6.9 ml h^{-1}; ns).[16] Two studies did not measure the number of patients who required interventions, rather they reported the amount of bupivacaine used in each group.[12 13] One of these studies reported that 'similar numbers' of patients required top-ups in each group.[12] The other reported an increased bupivacaine requirement in the PCEA group compared with CEI related to clinician top-ups.[13] This was statistically significant for first stage but not for the second stage or the total length of labour.

In addition to reporting the number of patients who required no interventions, three studies reported the total number of clinician top-ups in the CEI group compared with



Study (first author)	PCEA (*n/N*)	Infusion (*n/N*)	Risk difference (95% confidence interval)
Sia	17/20	16/20	
Butros	42/48	34/50	
Gambling	34/55	5/13	
Purdie	38/75	16/84	
Collis	27/44	12/46	
Curry	29/30	17/30	
Total (95% CI)	187/272	100/243	

Fig 1 The number of patients who required no unscheduled interventions by the clinician The RD and 95% CI for each study and the pooled estimates are shown. The size of the box represents the relative weight of each study, the lines represent the 95% CI The midpoint of the diamond is the pooled estimate of the RD. The diamond extends over the 95% CI of the pooled estimate.

PCEA. Tan and colleagues[8] found a significantly higher number in the CEI group than in the PCEA group (120 top-ups in 84 women compared with 49 in 75 women, respectively). Curry and colleagues[11] reported 27 top-ups in 30 patients who received CEI compared with only two top-ups in 30 patients who received PCEA ($P<0.001$). Sia and colleagues[15] reported six top-ups in 20 patients in the CEI group compared with three top-ups in 20 patients in the PCEA group during the first stage of labour ($P=0.4$).

Drug dose

The dose (mg h^{-1}) of local anaesthetic administered to patients receiving CEI was significantly greater than those in the PCEA group (Table 2). All studies that measured this outcome reported the same result regardless of whether bupivacaine or ropivacaine was used. The addition of opioid to the maintenance solution (either fentanyl or sufentanil) did not make a difference to this outcome. Because different regimen were used, this outcome is heterogeneous ($P<0.0001$) even though all studies favoured the PCEA group (Fig. 2).

Motor weakness

Motor power was measured in a number of different ways in each of the studies. Two studies reported 'no motor weakness' throughout the labour.[9 14] Two additional studies described no or minimal weakness at 2-h intervals over time.[10 15] We used the 2-h incidence of 'no weakness' in these studies for our analysis and found that this side-effect was significantly reduced in the PCEA group (Table 2). One study assessed motor power by asking the patient to sit up and then walk. However, the time at which this outcome was measured is not clear. The authors noted that all their patients, in both groups, could walk at some time during labour.[16]

Tan and colleagues[8] reported that patients receiving PCEA were more likely to have 'no motor weakness' compared with those having CEI, based on repeated assessments of each patient ($P<0.01$). The incidence of complete immobility of the lower extremities was not different between groups (4.5 *vs* 2.9%; ns). Two other studies found no difference between groups in 'dense motor block' as defined by Bromage scores of 2 or 3.[12 13]

Analgesia

Labour analgesia was measured at intervals using a visual or verbal analogue score (VAS) in seven studies,[9–15] and the number of distressing pain episodes in one.[7] These results were either displayed in graphic form or described qualitatively. The VAS scores were not different between groups in any of the studies. The numbers of distressing pain episodes were also similar. Finally, pain scores, when classified as mild, moderate or severe, were the same in both groups.[10]

One study specifically reported VAS scores for pain in the second stage of labour and found no difference between groups.[10] A second study reported that complete or good analgesia was also not significantly different between groups.[7] However, in this study 16.9% of women suffered 'unacceptable' pain in the PCEA group compared with 2.8% in the CEI group ($P=0.01$).

Patient satisfaction

Overall patient satisfaction with the method of analgesia, using a VAS score, was reported in five studies.[9–11 14 15] The data from four of these could be combined (Table 2). One study reported maternal satisfaction using a VAS scale at various times during labour and reported the data in graphical form, but did not report an overall score.[14] One study reported 'patient satisfaction with analgesia'.[7] These studies did not show a difference in maternal satisfaction between groups.

Obstetric and neonatal outcomes

The total length of labour (in minutes) was reported in three studies[9–11] and there was no difference between the groups. Similarly there was no difference in the duration of first stage of labour[12 13] or second one.[7 12 13 15] None of the studies reported a difference in the incidence of Caesarean section or instrumental delivery between groups. The incidence of low Apgar scores at 1 and 5 min after birth was low and similar in each group (Table 2).

Table 2 Summary of study outcomes. PCEA=patient-controlled epidural analgesia; CEI=continuous epidural infusion; WMD=weighted mean difference, RD=risk difference, CI=confidence interval

Outcome	Studies included (reference number)	PCEA (*n* or *n*/*N*)	CEI (*n* or *n*/*N*)	WMD or RD and 95% CI	*P*-Value
Mean dose of local anaesthetic	9–16	257	221	WMD: –3.92 (–5.38, –2.42)	<0.00001
Motor block: patients with no motor weakness	9, 10, 14, 15	151/167	103/129	RD: 18% (6%, 31%)	0.003
Maternal satisfaction: patients satisfied with technique	7	65/75	73/84	RD: 0% (–11%, 10%)	1
Maternal satisfaction: VAS scores	9–11, 15	139	144	WMD: 3.86 (–2.15, 9.88)	0.2
Pain relief: global pain assessment (VAS)	11	30	30	WMD: –7.20 (–19.16, 4.76)	0.2
Pain relief: pain of labour first stage (VAS)	10	40	44	WMD: 3.00 (3.00, –0.80, 6.80)	0.14
Pain relief: excellent analgesia first stage	7	47/75	54/84	RD: 2% (–17%, 13%)	0.8
Pain relief: no distressing pain in first stage	7	55/75	48/84	RD: 16% (2%, 31%)	0.03
Pain relief: complete or good analgesia in second stage	7, 15	62/95	62/104	RD: 5% (–8%, 18%)	0.5
Pain relief: pain assessment second stage (VAS)	10	41	44	WMD: 20.00 (7.44, 32.56)	0.02
Mode of delivery: Caesarean section	7, 9–16	41/333	51/307	RD: 4% (–8%, 1%)	0.12
Mode of delivery: instrumental deliveries	7, 9–16	19/333	98/307	RD: 1% (–6%, 7%)	0.9
Total length of labour	9–11	122	126	WMD: 7.68 (–65.75, 81.10)	0.8
Length of first stage	12, 13	35	35	WMD: 21.00 (–37.72, 79.71)	0.5
Length of second stage	7, 12, 13, 15	130	139	WMD: –10.33 (–21.59, 0.93)	0.07
Low Apgar score at 5 min	9, 10, 12–15	4/201	1/164	WMD: 0.01 (–0.02, 0.05)	0.5
Low Apgar score at 1 min	9, 10, 12–15	23/201	12/164	WMD: 0.00 (–0.07, 0.07)	1
Hypotension	9, 10, 12, 14–16	4/275	7/246	RD: –1% (–3%, 2%)	0.6
High sensory block	7, 9, 11	9/153	8/164	RD: 1% (–5%, 6%)	0.9
Shivering	15	5/20	4/20	RD: 5% (–21%, 31%)	0.7
Nausea	15	1/20	0/20	RD: 5% (–8%, 18%)	0.4
Pruritus	9, 12	11/68	7/70	RD: 3% (–15%, 21%)	0.8

Other outcomes

There was no difference between groups in the incidence of hypotension or high block (as described by any of the authors). The incidence of pruritus, shivering and nausea were similar in each group (Table 2).

Discussion

This systematic review shows that PCEA in labour consistently results in fewer clinician interventions when compared with CEI. This result was achieved using a lower dose of local anaesthetic but without any measurable change in pain relief or patient satisfaction. In addition, patients in most studies had better mobility in the PCEA group.

The need for unscheduled clinician interventions is an important outcome for a number of reasons, apart from simple convenience. Additional drug doses require opening the 'closed system' and may increase the risk of infection. Furthermore, it is usual for the clinician to use an increased drug dose compared with that available to the patient. If this dose is misplaced (either in the intravascular or intrathecal space), toxicity might result. Finally, because of the increased drug dose, motor block of the lower extremities may be more evident.

The use of less local anaesthetic is also an important advantage of PCEA. While this review did not show a difference in operative delivery between patients who received PCEA and those who received CEI, there is some evidence that drug dose may affect labour outcome. Recently, the COMET group[17] in the United Kingdom have shown that there is an increased incidence of operative vaginal delivery when conventional doses of local anaesthetic (0.25% bupivacaine) are used in labour compared with low dose techniques. Furthermore, cumulative doses of opioids, which are often combined with local anaesthetics in the infusions, may result in mild neonatal depression.[17] While none of the studies we have reviewed reported results from 'high' doses of local anaesthetics, it may still be an advantage to use less of the drugs.

The differences in patient mobility were also consistent between groups when this outcome was measured. This consistency was present despite the numerous ways in which motor weakness of the lower extremities was reported and was likely to have been a result of the observed increase in local anaesthetic dosage in the CEI group. Of note, in one study that used 0.1% ropivacaine and fentanyl 2 $\mu g\ ml^{-1}$, all patients could walk. It is possible that by reducing the concentration of local anaesthetic sufficiently, the difference in motor block between PCEA and CEI may become insignificant.

Of interest, although many of the studies reported measures of maternal satisfaction, there was no consistent difference between PCEA and CEI. This may be due to a number of reasons. First, satisfaction with both forms of analgesia appeared to be extremely high. Therefore, even by combining the results of all studies, the sample size may be insufficient to demonstrate a difference. This is particularly true because of the numerous different methods used to measure satisfaction and the different times (during labour or the next day) at which the question was asked. Second, it is very difficult to accurately measure maternal satisfaction. Often satisfaction with a particular technique is confused

Study (first author (yr))	PCEA (*n*)	Mean (SD)	Infusion (*n*)	Mean (SD)
Ferrante (1991)	20	9(4)	20	16(4)
Ferrante (1994)	15	9(4)	15	17(4)
Curry	30	8(3)	30	14(4)
Gambling	55	5(2)	13	9(3)
Sia	20	18(3)	20	21(5)
Collis	44	9(2)	46	12(3)
Butros	48	13(4)	50	15(4)
Smedvig	25	8(5)	27	8(0.4)
Total (95% CI)	257		221	

Weighted mean difference (95% confidence interval)

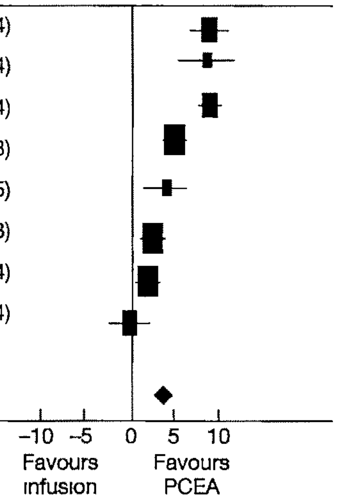


Fig 2 Dose of local anaesthetic. The weighted mean difference and 95% CI and pooled estimates are shown The size of the box represents the relative weight of each study, the lines represent the 95% CI. The midpoint of the diamond is the pooled estimate of the weighted mean difference. The diamond extends over the 95% CI of the pooled estimate

with satisfaction with pain relief. However, satisfaction is multidimensional and other factors such as patient expectations, communication skills of the health care team and the obstetric outcome are far more important than analgesia *per se*.[18] One study attempted to measure multiple aspects of satisfaction but still did not find any difference between groups.[10]

In this review, we found no difference between groups in the incidence of Caesarean section or instrumental vaginal delivery. Furthermore, there was no difference in the duration of either the first or second stages of labour. However, the studies were small and the total number of patients enrolled may have been insufficient. In addition, the combination of nulliparous and multiparous parturients in some of the studies would reduce the power to detect these outcomes. A single, large study with standardized obstetric management would be more likely to find a difference if it exists.

Both CEI and PCEA appear to be safe for the mother and neonate. The incidence of maternal side-effects and neonatal depression was extremely low in the studies that measured these outcomes. Maternal hypotension occurred in less than 3% of cases and a low 5 min Apgar score occurred in under 2% (Table 2). An extremely large series of patients would be required to determine if the two groups were different with respect to these outcomes.

In summary, PCEA for labour pain has several advantages when compared with CEI. These include a reduction in the number of unscheduled clinician top-ups, a reduction in the amount of drug used and a reduction in the amount of motor block of the lower extremities. Both methods are safe for the mother and newborn. More information is needed to determine which method of analgesia maintenance leads to a reduced need for obstetric intervention and better patient satisfaction.

Acknowledgement

We would like to thank Dr Barbara Leighton, Professor of Clinical Anesthesiology, Weill Medical College of Cornell University, New York, USA for her editorial assistance.

References

1 Glosten B. Epidural and spinal analgesia/anesthesia. In: Chestnut DH, ed. *Obstetric Anesthesia: Principles and practice*, 2nd edition. St Louis: Mosby, 1999; 360–86

2 Taylor HJ. Clinical experience with continuous epidural infusion of bupivacaine at 6 ml per hour in obstetrics. *Can Anaesth Soc J* 1983; **30**: 277–85

3 Gambling DR, Yu P, Cole C, McMorland GH, Palmer L. A comparative study of patient controlled epidural analgesia (PCEA) and continuous infusion epidural analgesia (CIEA) during labour. *Can J Anaesth* 1988; **35**: 249–54

4 Jadad AR, Moore RA, Carroll D, *et al.* Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; **17**: 1–12

5 Turhanoglu S, Ozyilmaz MA, Olmez G, Tok D, Bayhan N. Comparison of continuous epidural infusion and patient-controlled epidural analgesia in labour *Agri* 1999; **11**: 23–8

6 Uckunkaya N, Bilgin H, Sahin S, Ozarac O. Comparison of continuous infusion and patient-controlled epidural analgesia during labor. *Turk Anesteziyoloji Ve Reanimasyon* 1996; **24**: 19–23

7 Purdie J, Reid J, Thorburn J, Asbury AJ. Continuous extradural analgesia: Comparison of midwife top-ups, continuous infusions and patient controlled administration. *Br J Anaesth* 1992; **68**: 580–4

8 Tan S, Reid J, Thorburn J. Extradural analgesia in labour: complications of three techniques of administration. *Br J Anaesth* 1994; **73**: 619–23

9 Boutros A, Blary S, Bronchard R, Bonnet F. Comparison of intermittent epidural bolus, continuous epidural infusion and patient controlled-epidural analgesia during labor. *Int J Obstet Anesth* 1999; **8**: 236–41

10 Collis RE, Plaat FS, Morgan BM. Comparison of midwife top-ups, continuous infusion and patient-controlled epidural analgesia for maintaining mobility after a low-dose combined spinal-epidural. *Br J Anaesth* 1999; **82**: 233–6

11 Curry PD, Pacsoo C, Heap DG. Patient-controlled epidural analgesia in obstetric anaesthetic practice. *Pain* 1994; **57**: 125–7

12 Ferrante FM, Lu L, Jamison SB, Datta S. Patient-controlled epidural analgesia· demand dosing. *Anesth Analg* 1991; **73**. 547–552

13 Ferrante FM, Rosinia FA, Gordon C, Datta S. The role of continuous background infusions in patient-controlled epidural analgesia for labor and delivery. *Anesth Analg* 1994; **79**: 80–4

14 Gambling DR, Huber CJ, Berkowitz J, *et al.* Patient-controlled epidural analgesia in labour: varying bolus dose and lockout interval. *Can J Anaesth* 1993; **40**: 211–7

15 Sia AT, Chong JL. Epidural 0.2% ropivacaine for labour analgesia: parturient-controlled or continuous infusion? *Anaesth Intensive Care* 1999, **27**: 154–8

16 Smedvig JP, Soreide E, Gjessing L. Ropivacaine 1 mg/ml, plus fentanyl 2 microg/ml for epidural analgesia during labour. Is mode of administration important? *Acta Anasthesiol Scand* 2001; **45**: 595–9

17 Comparative Obstetric Mobile Epidural Trial (COMET) Study Group UK. Effect of low dose mobile *versus* traditional epidural techniques on mode of delivery: a randomized controlled trial. *Lancet* 2001; **358**. 19–23

18 Drew N, Salmon P, Webb L. Mothers', midwives' and obstetricians' views on the features of obstetric care which influence satisfaction with childbirth. *Br J Obstet Gynaecol* 1989; **96**: 1084–8

British Journal of Anaesthesia 89 (3) 466–72 (2002)

Epidural analgesia and backache: a randomized controlled comparison with intramuscular meperidine for analgesia during labour

B. A. Loughnan[1*], F. Carli[2], M. Romney[1], C. J. Doré[3] and H. Gordon[1]

[1]*Departments of Anaesthesia and Obstetrics and Gynaecology, Northwick Park Hospital, Watford Road, Harrow, Middlesex HA1 3UJ, UK.* [2]*Department of Anesthesia, McGill University, 681 Pine Avenue West, Montreal, Canada H3A 1A1.* [3]*Medical Research Council Clinical Trials Unit, 222 Euston Road, London NW1 2DA, UK*

**Corresponding author*

Background. Concern has been expressed that epidural analgesia for labour may be associated with a higher incidence of backache.

Methods. A prospective randomized trial investigating the effect of epidural analgesia on the outcome of labour in nulliparae, mothers were randomized to receive either epidural analgesia or meperidine. A questionnaire on postnatal symptoms was sent to them 6 months after delivery.

Results. In all, 611 mothers were studied; 310 were randomly allocated to receive i.m. meperidine up to 300 mg and 301 to receive epidural bupivacaine. The response rate to our questionnaire was 83%. Intention-to-treat analysis showed similar prevalence rates of postpartum backache in the epidural (48%) and meperidine groups (50%), with an observed difference (epidural–meperidine) of –2% (95% CI, –11 to +6%). After excluding mothers with backache before delivery, there were also similar incidence rates of postpartum backache in the epidural (29%) and meperidine groups (28%), observed difference 1% (95% CI, –8 to +10%).

Conclusions. Epidural analgesia in labour was not associated with an increase in the prevalence or incidence of backache.

Br J Anaesth 2002; **88**: 466–72

Keywords: anaesthetic techniques, epidural; analgesia, obstetric; analgesics opioid, meperidine; complications, backache

Accepted for publication: February 26, 2002

MacArthur and colleagues[1] reported an association between the development of new postpartum back pain and the administration of epidural analgesia in labour. However, their study was retrospective and relied on the mothers' recollections of events. Back pain has since been noted to be a common occurrence in pregnancy.[2] A more recent study suggested that epidural analgesia and the development of postpartum backache may be unrelated phenomena,[3] but there have been few large prospective randomized controlled trials to date that have compared the prevalence of backache in mothers who have received epidural analgesia with those who received meperidine for labour analgesia.

The present study is a randomized prospective comparison of the prevalence of backache in mothers who received epidural analgesia compared with mothers who had meperidine. Because other investigators[3 4] have noted the coexistence of other symptoms in association with backache, we also enquired about the presence of other symptoms.

Methods

The study was approved by the local research ethics committee and was designed as a part of a pragmatic randomized controlled trial comparing the outcomes of labour between mothers randomized to receive i.m. meperidine with those randomized to receive epidural analgesia for pain relief in labour.[5] Only nulliparous women with an open mind about their choice of analgesia were recruited to the study. They were approached by an experienced midwife in the later stages of pregnancy and agreed to be randomized with respect to their first analgesia.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

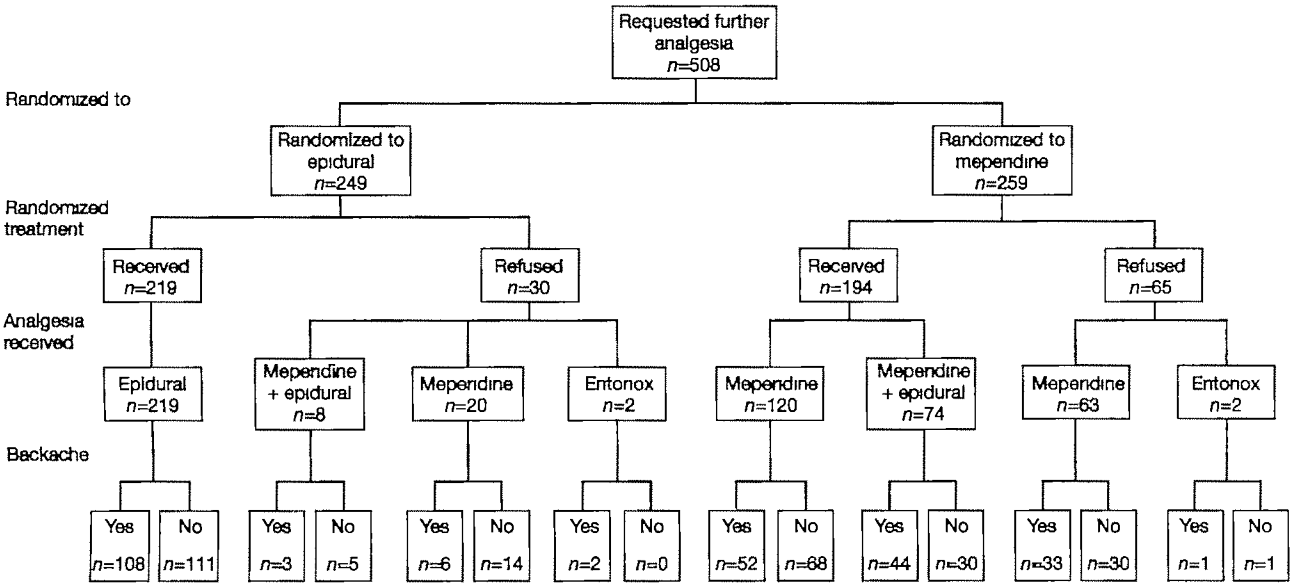


Fig 1 Flow diagram showing prevalence of back pain 6 months postpartum by analgesia received in labour by mothers who requested further analgesia and were randomized (n=611), returned the questionnaire (n=509) and answered the backache question (n=508)

On admission to the labour ward, the diagnosis of labour was confirmed. When requesting further analgesia, the envelope identifying their randomized treatment was opened and mothers were offered analgesia according to their randomization. They either received meperidine 100 mg by repeated i.m. injection (up to three doses), or a lumbar epidural was inserted and, after an initial dose of 0.25% bupivacaine 10 ml, an infusion of 0.125% bupivacaine was administered until the second stage of labour at the rate of 10–15 ml h^{-1} with top-ups of 0.25% bupivacaine 5 ml as required (this was the standard epidural analgesia administered on the labour ward at the time of the study commencement). For ethical reasons, the mothers were reassured at recruitment that they could opt out from the trial at any stage.

Twenty-four hours after delivery, the mothers were visited on the ward and asked about back pain and headache before and during pregnancy. For example, 'Did you suffer from backache?' and if 'yes', 'Was this during pregnancy, before pregnancy, or both?'.

Six months after delivery, a postal questionnaire was sent to the mothers. They were asked about a number of symptoms: frequent backache, frequent headaches or migraines, shoulder symptoms, neck symptoms, urinary incontinence and pain, tingling or weakness in the arms or legs. For each symptom they were asked whether it was present, when it had started and how it affected their daily functioning. For example, they were asked, 'Do you suffer from frequent backache?' and if 'yes', 'When did this first start? Was it before you became pregnant, during your pregnancy, or since you gave birth?'.

The two randomized groups were compared using Mann–Whitney U tests and Fisher's exact tests where appropriate. Analysis was performed comparing responders and non-responders to the 6-month questionnaire. We compared the groups on the basis of their treatment and also compared characteristics of the women who did and did not have new symptoms at 6 months postpartum.

Stepwise logistic regression was performed to investigate factors influencing the presence of each symptom, either as a persisting symptom or a new symptom 6 months postpartum. Possible predictor variables considered were randomized treatment, maternal age, height, weight, social class, marital status, ethnic group, induced labour, durations of first and second stages, oxytocin administration, mode of delivery, gestational age and foetal weight.

This study was part of a trial investigating the effect of epidural analgesia on Caesarean section rate.[5] The prospective sample size of 1168 for the trial had been calculated to detect a reduction in the Caesarean section rate from 7.8% in the epidural group (the observed rate in the unit in 1988) to a rate of 3.8% in the non-epidural group. We calculated that this sample size would also allow us to detect a difference in rates of chronic backache such as that reported by MacArthur and colleagues[1] for epidural (19%) and non-epidural (10.5%) with a power >99% and using a significance level of 5%. Recruitment to the trial was slower than anticipated and, of the planned 1168 mothers, 611 were randomized to receive either epidural analgesia (n=301) or i.m. meperidine (n=310) during labour.

Results

A total of 508 women returned the questionnaires 6 months after delivery, 249 of which had received the epidural and 259 had received meperidine. The overall response rate was

Table 1 Obstetric and patient characteristics of responders and non-responders to 6 months postpartum questionnaire. Summary statistics are median (interquartile range (IQR)) for continuous variables or frequencies (%) for categorical variables. *P*-values are from Mann–Whitney *U* test or Fisher's exact test

Variable	**Non-responders**		**Responders**		***P*-value**
	***n*/total *n* or median**	**% or IQR**	***n*/total *n* or median**	**% or IQR**	
Randomized treatment					
Epidural	51/102	50	250/509	49	0.9
Treatment received					0.6
Meperidine+epidural	17/102	17	82/509	16	
Epidural	50/102	49	282/509	55	
Meperidine	34/102	33	141/509	28	
Neither	1/102	1	4/509	1	
Age (yr)	25	22–29	27	24–30	0.02
Final weight (kg)	73	65–81	75	68–84	0.08
Height (cm)	163	158–167	162	158–166	0.4
Married	58/102	57	358/508	70	0.01
Caucasian	49/101	49	319/505	63	0.007
Social class I/II/III	67/100	67	379/496	76	0.06
Induced	32/101	32	153/504	30	0.8
First stage duration (h)	8.9	6.2–11.5	8.5	6.1–11.5	0.6
Second stage duration (h)	0.9	0.5–2.0	1.2	0.6–2.3	0.2
Syntocinon	55/102	54	305/507	60	0.3
Mode of delivery					0.5
Normal vaginal	67/102	66	300/509	59	
Instrumental	24/102	24	144/509	28	
Caesarean	11/102	11	65/509	13	
Gestational age (weeks)	40	39–41	40	39–41	0.8
Foetal weight (kg)	3.3	2.9–3.6	3.3	3.0–3.7	0.3

Table 2 Reported prevalence of backache 24 h and 6 months post delivery

24 h postpartum: 'Did you suffer from backache before delivery?'	**6 months postpartum: 'Do you suffer from frequent backache?' If 'yes', 'When did it first start?'**			**Total**
	Before delivery	**Since delivery**	**No frequent backache**	
Yes	109	58	111	278
No	25	43	143	211
Total	134	101	254	489

83%. There was no significant difference between the two randomized groups in terms of response rates, with 83 and 84% returned in the epidural and meperidine groups, respectively.

Of the 249 women who had been randomized to the epidural group, 219 received their randomized treatment (88%), while of the 259 women randomized to the meperidine group, 194 received their randomized treatment (75%). An intention-to-treat approach was used for the analysis, comparing women on the basis of their randomized treatment allocation. Figure 1 shows the prevalence of backache 6 months postpartum in the two randomized groups subdivided by the mode of analgesia actually received during labour, for mothers who requested further analgesia and were randomized (n=611), returned the questionnaire (n=509) and answered the backache question (n=508).

Table 1 compares the characteristics of the responders and non-responders to the 6-month postpartum questionnaire. There was no significant difference between patient characteristics of the groups in terms of treatment randomized, treatment received, labour characteristics or mode of delivery. However, married women were more likely to respond to the questionnaire (P= 0.01), as were older women (P=0.02) and Caucasians (P=0.007). There were no significant differences between the randomized groups in terms of these characteristics (results not shown).

There were 489 women who completed questionnaires at both 24 h and 6 months postpartum. They were asked about backache on both occasions. Table 2 shows the responses at 24 h and 6 months postpartum. Many of the women gave inconsistent responses. There were 58 mothers who had stated 24 h postpartum that they had suffered from backache before delivery but stated at the 6-month follow-up that their backache had only commenced after delivery. There were also 25 mothers who said at 24 h that they had not had antepartum backache but at 6 months stated that their backache had commenced before delivery.

Table 3 Prevalence of symptoms 6 months postpartum. Summary statistics are frequencies (%). *P*-values are from Fisher's exact test

Symptom	Epidural		Meperidine		*P*-value
	n/total *n*	%	*n*/total *n*	%	
Backache	119/249	48	130/259	50	0.6
Headache	56/248	23	68/256	27	0.3
Neck ache	60/247	24	70/256	27	0.5
Urinary incontinence	46/246	19	51/258	20	0.8
Arm symptoms	36/244	15	49/255	19	0.2
Leg symptoms	51/243	21	46/246	19	0.6

Table 4 Incidence of new symptoms 6 months postpartum. For each symptom, the table shows its occurrence in patients not suffering the particular problem antepartum. Hence the variable numbers of subjects in the epidural and meperidine groups within the table. Summary statistics are frequencies (%). *P*-values are from Fisher's exact test

Symptom	Epidural		Meperidine		*P*-value
	n/total *n*	%	*n*/total *n*	%	
Backache	52/182	29	49/178	28	0.9
Headache	26/218	12	25/213	12	1.0
Neck ache	32/219	15	37/223	17	0.6
Urinary incontinence	26/226	12	33/240	14	0.5
Arm symptoms	22/230	10	28/234	12	0.5
Leg symptoms	26/218	12	23/223	10	0.7

The prevalence of each postnatal symptom at 6 months in the two randomized groups is compared in Table 3. There was no significant difference between the two randomized groups in the frequency of any of the symptoms enquired about. There was also no significant difference in the prevalence of backache between the epidural and meperidine groups (48 *vs* 50%), with an observed difference in backache prevalence (epidural–meperidine) of −2.4% (95% CI, −11.1 to +6.3%).

In the stepwise logistic regression models to predict the presence of each symptom at 6 months, there was a positive relationship between the occurrence of backache and duration of the first stage (odds ratio (OR) for a 1 h increase, 1.08; 95% CI, 1.03–1.14; P=0.002). With respect to headaches, there was a positive relationship with non-Caucasian ethnic groups (OR, 1.70; 95% CI, 1.07–2.71; P=0.03) and a negative relationship with maternal age (OR, 0.94 for a 1 yr increase in age; 95% CI, 0.89–0.99; P=0.02). For urinary incontinence, there was a positive relationship with instrumental delivery (OR, 1.72; 95% CI, 1.04–2.84; P=0.03). For pain, tingling or weakness in the arms there was a negative relationship with maternal height (OR, 0.94 for a 1 cm increase in height; 95% CI, 0.90–0.99; P=0.01), a positive relationship with length of first stage (OR, 1.07 for a 1 h increase; 95% CI, 1.01–1.15; P=0.03) and a positive relationship with non-Caucasian ethnic group (OR, 2.49; 95% CI, 1.38–4.47; P=0.002). For pain, tingling or weakness in the legs there was also a positive relationship with non-Caucasian ethnic group (OR, 2.82; 95% CI, 1.70–4.69; P<0.001).

Table 4 is a comparison between the two randomized analgesia groups after omitting women who stated 6 months postpartum that the symptoms began before or during pregnancy. There were no significant differences between the two randomized groups in the incidence of any new postpartum symptoms. The incidence of new backache in the epidural group was 29% and in the meperidine group 28%, with an observed difference in the incidence of backache (epidural–meperidine) of 1.0% (95% CI, −8.2 to +10.3%). Other new symptoms such as headache, neck ache, urinary incontinence, and arm or leg symptoms were reported by around 12% of each group.

Stepwise logistic regression analysis performed to predict whether or not a woman had each new symptom showed relationships similar to those found when predicting the presence of any symptoms. There was a negative relationship between headache and maternal age (OR, 0.89 for a 1 yr increase; 95% CI, 0.81–0.97; P=0.007) and a positive relationship with being married (OR, 2.36; 95% CI; 1.00–5.55; P=0.05). There was a positive relationship between urinary incontinence and oxytocin administration (OR, 2.36; 95% CI, 1.17–4.77; P=0.02) and a positive relationship with instrumental delivery (OR, 1.86; 95% CI, 1.00–3.45; P=0.05). For arm symptoms, there was a negative relationship with maternal height (OR, 0.94; 95% CI, 0.89–0.99; P=0.03) and a positive relationship with non-Caucasian ethnic group (OR, 3.85; 95% CI, 1.84–8.07; P<0.001). For leg symptoms there was a positive relationship with non-Caucasian ethnic group (OR, 2.24; 95% CI, 1.18–4.27; P=0.01).

Table 5 Obstetric and patient characteristics of those with new backache 6 months postpartum and those who had never had backache. Summary statistics are median (IQR) for continuous variables or frequencies (%) for categorical variables *P*-values are from Mann–Whitney *U* test or Fisher's exact test

Variable	**No backache**		**Backache**		***P*-value**
	***n*/total *n* or median**	**% or IQR**	***n*/total *n* or median**	**% or IQR**	
Randomized treatment					
Epidural	130/259	50	52/101	51	0.9
Treatment received					0.02
Meperidine+epidural	35/259	14	20/101	20	
Epidural	141/259	54	62/101	61	
Meperidine	82/259	32	18/101	18	
Neither	1/259	1	1/101	1	
Age (yr)	27	24–30	27	24–30	1.0
Final weight (kg)	74	68–83	74	66–84	0.8
Height (cm)	163	159–167	162	157–166	0.09
Married	181/259	70	75/101	74	0.4
Caucasian	172/259	66	52/100	52	0.02
Social class I/II/III	190/250	76	81/99	82	0.3
Induced	75/255	30	34/100	34	0.4
First stage (h)	8	5.5–11	9.8	7.5–12.8	0.001
Second stage (h)	1.2	0.7–2.1	1.1	0.6–2.2	1.0
Syntocinon	148/258	57	66/101	65	0.19
Mode of delivery					0.3
Normal vaginal	162/259	63	54/101	53	
Instrumental	66/259	25	31/101	31	
Caesarean	31/259	12	16/101	16	
Gestational age (weeks)	40	39–41	40	39–41	0.3
Foetal weight (kg)	3.3	3.0–3.7	3.2	3.0–3.5	0.1

Table 5 compares the characteristics of women with and without new backache at 6 months postpartum, excluding those with backache before delivery. There were no significant differences between the groups in terms of randomized treatment allocated. However, there was a significant difference between groups in the type of analgesia actually received (P=0.02); women with new backache were more likely to have had epidural analgesia. The proportion of non-Caucasian women was higher in those who developed new backache (P=0.02) and the duration of first stage was longer (P=0.001).

Stepwise logistic regression was performed to predict whether a woman developed new backache. There was a positive relationship between new backache and non-Caucasian ethnic group (OR, 1.73; 95% CI, 1.02–2.94; P=0.04), and a positive relationship with duration of first stage (OR, 1.11 for a 1 h increase; 95% CI, 1.04–1.18; P=0.002), but no significant relationship with type of analgesia received.

Discussion

We have shown, like other investigators, that backache is an extremely common complaint postpartum and was present in 49% of mothers 6 months after delivery. When groups were compared on the basis of their randomized treatment allocation, there was no significant difference in the prevalence of backache between the epidural (48%) and meperidine (50%) groups. Our study was designed on a randomized prospective basis. In other non-randomized studies, the presence of backache or the choice of analgesia in labour may influence the mothers' reporting of back pain.

Our comparison between the two analgesia groups was performed on an intention-to-treat basis as this is the least biased approach.[6] There was no significant difference between the groups when they were compared on this basis; the incidence of new backache in the epidural group was 29% and in the meperidine group 28%.

When we compared those with new backache at 6 months with those who had never had backache (Table 5), the type of analgesia actually received was significantly different. Epidural administration was more common in those with new backache (82 out of 101 patients; 81%) than those without (176 out of 259; 68%). This is consistent with the finding of McQuay and colleagues[7] who suggest a small but slight increase in the development of new backache after epidural administration. However, this was based on a systematic review of results from non-randomized studies and would therefore incorporate any biases occurring in such studies. In our stepwise logistic regression model, the type of analgesia was no longer a significant predictor after including the duration of the first stage of labour and Caucasian ethnic group in the model. Our findings are similar to those of Howell and colleagues.[8]

In our study, the prevalence of backache in the meperidine group was 50% and in the epidural group was 48%. This differs considerably from the rate of new backache of 10.5% in the non-epidural group and rate of 19% in the epidural group in the retrospective study by MacArthur and colleagues,[1] used in our prospective power calculation. When a *post-hoc* power calculation was performed for our study, it showed that we would have needed a sample size of 1605 in each group to detect a 5% difference in the prevalence of backache (50 *vs* 45%) using the 5% significance level with a power of 80%. This is beyond the scope of most institutions and could only be performed in a large multi-centre trial.

The response rate to our questionnaire was high (83%). This compares favourably with the 40% response rate of MacArthur and colleagues[1] and the 63% response rate of Russell and colleagues[9] and is similar to the 88% response rate of Breen and colleagues.[4] Of some concern is the fact that the responders were more likely to be Caucasian and married than the non-responders were. Our study showed a positive relationship between non-Caucasian status and the presence of back pain and other postnatal symptoms such as arm and leg symptoms. It is possible that this effect could be due to non-Caucasian women with postnatal symptoms being more likely to respond than those without postnatal symptoms. However, in a study by Russell and colleagues,[9] European and West Indian women were more likely to respond than other groups.

The prevalence of backache at 6 months in our study (49%) is similar to the prevalence of 44% found by Breen and colleagues[4] at 2 months postpartum, but considerably greater than the 30% found by Russell and colleagues[9] at 12 months. The incidence of new backache at 6 months is somewhat less common (28%) in our study, while that of Russell and colleagues[9] was 15% at 12 months. Russell and colleagues' study was retrospective but suggests that the prevalence of postpartum backache may be lower at 12 than at 3 or 6 months after delivery. We chose a 6-month follow-up period as back pain is particularly relevant when the mother is weaning her child and possibly planning to return to employment.

There was a higher proportion of non-Caucasian women (35%) who developed new backache compared with Caucasian women (23%). Non-Caucasian women also developed other symptoms postpartum. Our local population, from which the study sample was taken, is comprised of 25% Gujerati Asians. Although theirs was a retrospective study, MacArthur and colleagues[10] found that backache, frequent headache, shoulder ache and pains and weakness in the arms and legs all occurred more commonly among Asian than among Caucasian women. Russell and colleagues[9] did not report the incidence of new backache with respect to other symptoms or to ethnic group, but did state that, of 36 women seen with new backache, 14 had possible psychological factors related to the backache. Our high prevalence of backache compared with other studies may be due to our study population. MacArthur and colleagues[10] postulate that dietary factors may play a role in the prevalence of postpartum problems among Asian women; the cause of backache in Asian women may be of dietary or sociological origin and warrants further investigation.

The mothers gave inconsistent replies to the questionnaires 24 h and 6 months postpartum and this finding draws attention to possible problems associated with the interpretation of retrospectively collected data on postpartum backache. Russell and colleagues[9] found that memories even at 18 months postpartum were unreliable. This calls into question the findings of MacArthur and colleagues[1] who found an association between epidural analgesia and backache but relied on the mothers' memories of events as long as 11 yr previously. In a later prospective study MacArthur and colleagues[11] found that although the incidence of low backache was significantly higher in the epidural group than in the non-epidural group on day 1, there was no significant difference at 7 days or 6 weeks.

Our study, like that of Russell and colleagues[9], is restricted to nulliparous women. The studies of MacArthur and colleagues[1] and Breen and colleagues[4] included multiparae. The disadvantage of including multiparae in a study on backache is that back pain may have occurred in relation to a previous pregnancy.

In summary, we have shown that back pain is a common symptom 6 months postpartum and the incidence of new back pain was 28%. In a randomized prospective controlled trial, there was no significant difference in the prevalence between epidural and meperidine groups when an intention-to-treat analysis was used. Women can be reassured that the administration of an epidural *per se* is unlikely to cause backache.

Acknowledgement

The authors wish to acknowledge the financial support of the National Health Service Executive North Thames (Previously the North West Thames Regional Health Authority Locally Organised Research Scheme)

References

1 MacArthur C, Lewis M, Knox EG, Crawford JS Epidural anaesthesia and long term backache after childbirth. *Br Med J* 1990, **301**: 9–12

2 MacEvilly M, Buggy D. Back pain and pregnancy· a review. *Pain* 1996; **64**: 405–14

3 Russell R, Dundas R, Reynolds F Longterm backache after childbirth: prospective search for causative factors *Br Med J* 1996; **312**: 1384–8

4 Breen TW, Ransil BJ, Groves PA, Oriol NE. Factors associated with back pain after childbirth *Anesthesiology* 1994, **81**. 29–34

5 Loughnan BA, Carli F, Romney M, Doré CJ, Gordon H Randomized controlled comparison of epidural bupivacaine *versus* pethidine for analgesia in labour *Br J Anaesth* 2000, **84**. 715–9

6 Newell DJ. Intention-to-treat analysis: implications for quantitative and qualitative research. *Int J Epidemiol* 1992; **21**. 837–41

7 McQuay H, Moore A. Epidural anaesthesia and low back pain after delivery. *Br Med J* 1996; **312**. 581

8 Howell CJ, Kidd C, Roberts W, *et al.* A randomised controlled trial of epidural compared with non-epidural analgesia in labour *Br J Obstet Gynaecol* 2001; **108**: 27–33

9 Russell R, Groves P, Taub N, O'Dowd J, Reynolds F. Assessing long term backache after childbirth. *Br Med J* 1993; **306**: 1299–303

10 MacArthur C, Lewis M, Knox EG. Comparison of long-term health problems following childbirth among Asian and Caucasian mothers. *Br J Gen Pract* 1993; **43**: 519–22

11 MacArthur A, MacArthur C, Weeks S. Epidural anaesthesia and low back pain after delivery: a prospective cohort study. *Br Med J* 1995; **311**: 1336–9

British Journal of Anaesthesia **89** (3): 473–8 (2002)

Management of post-strabismus nausea and vomiting in children using ondansetron: a value-based comparison of outcomes†

B. Sennaraj[1], D. Shende[1], S. Sadhasivam[2]*, S. Ilavajady[3] and D. Jagan[1]

[1]All India Institute of Medical Sciences, New Delhi, India. [2]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA. [3]Northern General Hospital, Sheffield Teaching Hospital NHS Trust, Sheffield, UK.

**Corresponding author: Department of Anesthesia, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Harvard Medical School, Boston, MA 02115, USA*

Background. This study evaluated the clinical efficacy and cost-effectiveness of prophylactic ondansetron versus early ondansetron treatment in the management of postoperative nausea and vomiting (PONV) in children undergoing strabismus repair using clinically meaningful outcomes and value-based principles.

Methods. One hundred and fifty children were randomly assigned to either prophylactic (P) or early symptomatic treatment only (T) group (n=75). Children in group P received ondansetron 100 $\mu g\ kg^{-1}$ i.v. and those in group T received placebo at the end of the procedure. After surgery, at the earliest sign of nausea or vomiting, children in both groups received ondansetron 100 $\mu g\ kg^{-1}$ i.v. Besides the incidence of PONV, non-surrogate (fast tracking time, duration of stay in the postanaesthesia care unit (PACU) and parental satisfaction scores), therapeutic (numbers needed to prevent and treat) and pharmacoeconomic (cost to benefit a child and cost per PONV-free child) outcome measures were evaluated.

Results. The incidences of PONV in the immediate, early, late and first 24-h periods were significantly less in group P (20, 12, 19 and 35% respectively) than in group T (37, 29, 47 and 72%, P<0.05). Time to achieve fast-track eligibility and duration of PACU stay were significantly shorter in group P (P<0.001). Children in group P had superior mean (SD) parental satisfaction scores (8.2 (1.8)) compared with those in group T (6.8 (1.7), P<0.001). The number needed to prevent PONV was 2 and the number needed to treat PONV was 9. The cost to benefit a child was more than fourfold less and the cost per PONV-free child was 35% less in group P.

Conclusions. Compared with early symptomatic treatment with ondansetron, prophylactic ondansetron shortened fast-tracking time and duration of PACU stay and improved parental satisfaction and therapeutic outcomes at a lower direct cost.

Br J Anaesth 2002; **89**: 473–8

Keywords: vomiting, postoperative nausea and vomiting; vomiting, antiemetics, ondansetron; anaesthesia, audit

Accepted for publication: March 6, 2002

Controversy in the management of postoperative nausea and vomiting (PONV) continues despite the availability of effective and newly developed antiemetics. This is mainly because of the multifactorial aetiology of PONV, different risks of PONV in different patient populations, different antiemetic approaches and different desired outcomes. A recent clinical trial[1] in children undergoing strabismus repair which evaluated clinically more important non-surrogate[2] and therapeutic outcome measures[3] recommended the practice of prophylactic administration of ondansetron. However, in adult patients undergoing outpatient surgery, prophylaxis with ondansetron had been shown not to improve outcomes when compared with early symptomatic treatment.[4] There is no clinical evidence to recommend the use of prophylactic ondansetron rather than

---

†This work was supported by institutional and departmental sources The study was presented at the annual meeting of American Society of Anesthesiologists.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

treating patients early at the first episode of PONV in a homogeneous high-risk population.

This trial evaluated the effectiveness of prophylactic ondansetron versus early treatment of PONV with ondansetron in children undergoing strabismus repair, a population with a high risk of PONV. Fast track eligibility time, duration of stay in the postanaesthesia care unit (PACU), parental satisfaction and therapeutic and pharmacoeconomic outcome measures were also compared.

Methods

After obtaining institutional review board approval and informed parental consent, in this prospective, randomized, double-blind study, we enrolled and studied 150 children (ASA I or II, aged 2–15 yr) undergoing strabismus repair under general anaesthesia. We excluded children who received drugs known to have antiemetic effects (e.g. phenothiazines, benzamides, scopolamine, corticosteroids, tricyclic antidepressants) in the 24 h before surgery. Children did not consume milk or solid food for at least 6 h before operation; clear fluids were allowed until 3 h before induction.

Children were not premedicated. Anaesthesia was induced with halothane and nitrous oxide in oxygen via a facemask or with i.v. thiopental. After induction of anaesthesia and establishment of venous access, tracheal intubation was facilitated with vecuronium 100 $\mu g\ kg^{-1}$ i.v., and anaesthesia was maintained with halothane and 66% nitrous oxide along with meperidine 0.5 $mg\ kg^{-1}$ i.v. A random number generator was used to assign each child prospectively to either the prophylactic (P) or the therapeutic (T) group (n=75). At the end of the procedure (when the last extraocular muscle was repaired), children in group P received ondansetron 100 $\mu g\ kg^{-1}$ i.v. (maximum of 4 mg) and children in group T received saline. The study drugs were prepared by an anaesthetist not directly involved in patient care, to a fixed volume of 5 ml to maintain the double-blind nature of the study.

Intraoperative i.v. fluid management consisted of administration of lactated Ringer's solution sufficient to correct half of the preoperative fluid deficit in the first hour, followed by maintenance fluids according to body weight. At the end of the procedure, residual neuromuscular blockade was antagonized with neostigmine 50 $\mu g\ kg^{-1}$ and glycopyrrolate 10 $\mu g\ kg^{-1}$ and the trachea was extubated when the child was awake.

All children were transported to the PACU, where they stayed for a minimum of 2 h for initial evaluation and management and for assessment of eligibility for fast tracking. One of the study personnel assessed postanaesthetic recovery, using a modified Aldrete's scoring system,[5] and the time to achieve eligibility for fast tracking [6] (fast tracking time, FTT). Time to achieve complete recovery (a modified Aldrete recovery score of 10) was recorded for all children. FTT was calculated as the time from the discontinuation of anaesthesia to the time at which a child had patent airway without support, no PONV and pain, and a modified Aldrete recovery score of 10. The criteria for discharge from the PACU to the ward included stable vital signs, adequate pain control and no nausea and vomiting in the first 2 h after surgery. Children who had PONV and/or pain were observed in the PACU until they had been free of PONV and pain for 1 h.

All episodes of PONV in the first 24 h in the hospital were recorded at intervals of 0–2, 2–6 and 6–24 h by the PACU and ward nursing staff, who were aware of the nature of the study but blinded to the study drug. We did not assess nausea in younger children (less than 6 yr of age). In older children, nausea was assessed by an observer asking the child whether he or she had any nausea, in addition to self-reporting. Any child having an episode of vomiting or nausea was treated with ondansetron 100 $\mu g\ kg^{-1}$ i.v. (maximum 4 mg) as the first postoperative antiemetic. If ondansetron failed to control nausea and vomiting in 30 min, metoclopramide 150 $\mu g\ kg^{-1}$ and promethazine 0.5 $mg\ kg^{-1}$ were used as the rescue antiemetics (second and third choices respectively).

Postoperatively, analgesia was provided when older children complained or younger children cried in pain.[7] Oral ibuprofen 10 $mg\ kg^{-1}$ was administered as the analgesic of first choice and, for pain in children who had PONV, ketorolac 0.5 $mg\ kg^{-1}$ i.v. was administered as the analgesic of second choice. Intravenous fluid consisted of lactated Ringer's solution to replace the fluid deficit plus maintenance fluids in the recovery room.

Finally, at the end of 24 h after surgery, the health-care worker who stayed with the child for most of the time was asked to give a global assessment of satisfaction over the entire postoperative experience of the child on the basis of the presence or absence of nausea, vomiting, pain and other adverse events. Parental satisfaction scores were obtained using an 11-point verbal linear numerical scoring system (0=not at all satisfied, 10=fully satisfied).

Power analysis before the study showed that 68 children would be required in each group to give an 80% chance (β=0.2) of detecting a 25% absolute reduction in the incidence of PONV between the groups for a basal PONV incidence of 55% with a type-1 error of 5% (Epi Info, version 6.04b; Center for Disease Control, Atlanta, GA, USA and World Health Organization, Geneva, Switzerland, 1997).

Two sample t-tests and the Mann–Whitney U-test were used to compare the age, weight, durations of anaesthesia, recovery and PACU stay, FTT, perioperative fluid and analgesic requirements and parental satisfaction. The incidences of PONV and rescue antiemetic requirements were compared by the χ^2 and Fisher's exact tests with Yates' continuity correction wherever appropriate. The positive numbers needed to prevent and treat (NNP and NNT) PONV were calculated as the reciprocals of absolute risk reductions of incidences of PONV from our institute's

Table 1 Patient characteristics and clinical data. Gender, ASA status, previous PONV, oculocardiac reflex (OCR) and postoperative analgesic requirements are expressed as the number of children. Other values are expressed as mean (SD or range). No significant differences

	Prophylactic group (*n*=75)	**Symptomatic treatment group** (*n*=75)	*P*
Age (yr)	6.9 (2–15)	6.3 (2–14)	0.32
Gender (M/F)	29/46	33/42	0.51
Weight (kg)	22.2 (8.5)	21.3 (9.9)	0.30
ASA physical status I, II	67, 8	69, 6	0.78
Prior PONV	12/75	9/75	0.64
Induction (halothane/thiopental)	57/18	61/14	0.55
OCR requiring atropine	11/75	8/75	0.46
Intraoperative			
Fluids (ml kg^{-1})	16.1 (3.9)	16 (4.5)	0.85
Meperidine (mg)	11.2 (4.1)	10.8 (4.8)	0.67
Number of muscles			
1	12/75	17/75	0.41
2	45/75	42/75	0.74
3	14/75	10/75	0.50
4	4/75	6/75	0.74
Duration of anaesthesia (min)	61.8 (13.0)	66.5 (20.9)	0.10
Recovery time (min)	10.3 (6.79)	11.9 (6.7)	0.10
Postoperative analgesia			
0–2 h	11/75	15/75	0.52
0–24 h	63/75	57/75	0.31

basal incidence of 83%[1] for children who received ondansetron prophylactically and early symptomatic treatment respectively. Similarly, the number needed to improve satisfaction (NNS) was calculated as the reciprocal of the absolute percentage of unsatisfied parents (parental satisfaction score <7.5).

The cost to benefit a child was calculated as the drug (ondansetron) acquisition cost per child multiplied by NNT (treatment) or NNP (prevention). The ondansetron acquisition cost per child was calculated by multiplying its acquisition cost in our institution by the mean weight (kg) of the children in each group. For the pharmacoëconomic analysis, we assumed the institutional acquisition costs of 1 mg of ondansetron, 10 mg of metoclopramide and 25 mg of promethazine as US$4, US$0.29 and US$1.25 respectively. The direct antiemetic cost per PONV-free child was calculated by dividing the total acquisition costs of all antiemetics administered (including ondansetron administered prophylactically in group P) by the number of PONV-free children in each group.

Results

Age, gender, weight, ASA physical status, children with a history of prior PONV, children who were induced with halothane and thiopental, children who required atropine to manage oculocardiac reflex, duration of procedure, perioperative fluid and analgesic requirements, were similar in the two groups (Table 1).

The incidence of PONV and nausea alone over 24 h was significantly lower in the prophylactic ondansetron group than in the therapeutic ondansetron group ($P<0.001$) (Table 2). The incidences of PONV in the immediate (20 *vs* 37.3%, $P=0.03$), early (12 *vs* 29.3%, $P=0.015$) and late (18.7 *vs* 46.7%, $P<0.001$) postoperative periods were significantly lower in the prophylactic ondansetron group (Table 2). The incidences of nausea alone in the immediate (20.5 *vs* 53.8%, $P=0.0016$), early (11.4 *vs* 43.6%, $P=0.0021$) and late (20.5 *vs* 61.5%, $P=0.001$) postoperative periods were significantly lower in the prophylactic group (Table 2). The requirements for rescue antiemetics in different epochs were significantly less in the prophylactic group (Table 2).

The positive NNP PONV was 2 in the prophylactic ondansetron group (NNP=2) and 9 in the early symptomatic treatment group (NNT=9) (Table 3). The requirement for rescue antiemetics to manage PONV in the early and the late postoperative periods was significantly less with prophylaxis than with early symptomatic treatment ($P<0.001$) (Table 2).

The duration of recovery and requirements for postoperative analgesics were comparable in the two groups (Table 1). The FTT in the prophylactic ondansetron group was shorter than that in the therapeutic ondansetron group (21.6 (4.1) *vs* 28.2 (5.3) min, $P<0.0001$). The duration of PACU stay was significantly longer in the therapeutic group than in the prophylactic ondansetron group (141.1 (30.6) *vs* 126.5 (13.9) min, $P=0.0002$) (Table 3). The incidence of headache was comparable in the two groups (12 *vs* 8%, $P=0.6$).

Children in the prophylactic ondansetron group had significantly higher parental satisfaction scores than those in the therapeutic group (8.2 (1.8) *vs* 6.8 (1.7), $P<0.001$) (Table 3). More parents of children in the prophylactic ondansetron group had greater satisfaction (score of 7.5 or

Table 2 Incidence and severity of PONV. Values are expressed as the number (percentage) of children

PONV outcome	**Prophylactic group** (*n*=75)	**Symptomatic treatment group** (*n*=75)	***P***
PONV incidence			
0–2 h	15/75 (20%)	28/75 (37.3%)	0.0303
2–6 h	9/75 (12%)	22/75 (29.3%)	0.0155
6–24 h	14/75 (18.7%)	35/75 (46.7%)	0.0005
0–24 h	26/75 (34.7%)	54/75 (72%)	<0.0001
Nausea incidence			
0–2 h	9/44 (20.5%)	21/39 (53.8%)	0.0016
2–6 h	5/44 (11.4%)	17/39 (43.6%)	0.0021
6–24 h	9/44 (20.5%)	24/39 (61.5%)	0.0001
0–24 h	18/44 (40.9%)	30/39 (76.9%)	0.0009
Rescue requirements			
0–2 h	15/75 (20%)	28/75 (37.3%)	0.0303
2–6 h	9/75 (12%)	22/75 (29.3%)	0.0155
6–24 h	14/75 (18.7%)	35/75 (46.7%)	0.0005
0–24 h	26/75 (34.7%)	54/75 (72%)	<0.0001
Rescue antiemetics			
First ondansetron	26/75 (34.7%)	54/75 (72%)	<0.0001
Second. metoclopramide	7/75 (9.3%)	22/75 (29.3%)	0.0019
Third promethazine	2/75 (2.7%)	10/75 (13.3%)	0.0351

Table 3 Therapeutic and pharmacoeconomic outcome measures NNP PONV and side-effects are expressed as the number of children Other values are expressed as mean (SD). NNP=number needed to prevent; NNT=number needed to treat; NNS=number needed to improve satisfaction, PONV=postoperative nausea and vomiting; PACU=postanaesthesia care unit; FTT=fast tracking time

Outcome measure	**Prophylactic group** (*n*=75)	**Symptomatic treatment group** (*n*=75)	***P***
FTT (min)	21.6 (4.1)	28.2 (5.3)	<0.0001
PACU stay (min)	126.5 (13.9)	141.1 (30.6)	0.0002
NNP/NNT PONV	2	9	–
NNS	1.6	4	
Parental satisfaction score	8.2 (1.8)	6.8 (1.7)	<0.0001
Cost to benefit a child (US$)	17.8	76.7	–
Cost per PONV-free child (US$)	21.3	28.9	–

more) than parents of children in the therapeutic ondansetron group (64 *vs* 25.3%, *P*<0.0001). The positive number needed to improve satisfaction (NNS) was 3.95 in the early treatment group and 1.56 in the prophylactic group.

The cost to benefit a child with ondansetron was US$17.8 in the prophylactic group and US$76.7 in the early therapeutic group. The total direct cost of all antiemetics per PONV-free child was 35.5% less with prophylactic ondansetron (US$21.3) than with early treatment (US$28.9).

Discussion

In our study, ondansetron administered prophylactically reduced the time to achieve fast track eligibility and the duration of PACU stay, outcomes with potential for perioperative cost reduction. Prophylactic ondansetron also improved parental satisfaction and the number needed to benefit a child. In addition, there was a significant reduction in the direct cost with the use of prophylactic ondansetron. The incidence of PONV and the need for rescue antiemetics were significantly less in the prophylactic compared with the early treatment group. The increased need for metoclopramide and promethazine as rescue antiemetics in the therapeutic ondansetron group reflects the fact that ondansetron is not as effective against established PONV as it is in preventing PONV. In this trial, the two groups were comparable with respect to patient characteristics, surgical procedure, anaesthetics, perioperative analgesics and i.v. fluids. Therefore, the difference in the outcome measures between the two groups can be attributed directly to the difference in ondansetron administration.

Strabismus repair is associated with the highest risk of PONV in children.[1 8] Routine prophylactic use of ondansetron has been demonstrated recently to improve true outcome measures after strabismus repair in children, as well as reducing the incidence of PONV.[1] However, prophylaxis with ondansetron in a heterogeneous (varying PONV risk) adult population undergoing ambulatory surgery has been shown not to improve outcomes after outpatient surgery compared with early symptomatic treatment.[4] Our study, in a homogeneous population of children with a high risk of PONV, demonstrated that prophylactic ondansetron was more effective than the early treatment.

Most studies on PONV reported only surrogate measures, such as the incidence of PONV and the number of emetic episodes per patient. Use of surrogate outcomes alone in PONV studies has been criticized.[2] In our trial, we used parental satisfaction scores for the child's perioperative experience, the duration of PACU stay and FTT as the true outcome measures. In addition, we evaluated the number needed to treat and prevent PONV.[3] The NNT was 9 but the NNP was 2, indicating that alternate children benefited from prophylactic ondansetron.

Fast tracking after general anaesthesia, which has cost-reducing potential, involves transferring patients directly from the operating room to a less labour-intensive step-down unit. The time to reaching eligibility for fast tracking was shorter in the prophylactic group compared with the treatment group (Table 3). The shorter FTT in the prophylactic group can be attributed to the significant reduction in the incidence of PONV in the immediate postoperative period and the decreased need for rescue antiemetics. Transfer of patients directly from the operating room to a less labour-intensive recovery area may decrease costs.[9 10] The children in our study stayed in the hospital for 24 h for social and health-care access reasons and we utilized this extended stay to assess the safety of fast tracking and to assess late PONV. Early and safe fast tracking achieved with prophylactic ondansetron reveals its cost-saving potential in this high-risk population. The FTT could have been even shorter in our study had we used propofol and sevoflurane, which were not available to us at the time of this study. As it is unusual to keep children in hospital for 24 h after strabismus surgery in other parts of the world, in order to make our findings relevant to others we measured FTT and the duration of PACU stay when we analysed cost–benefit.

PONV after ambulatory surgery is one of the leading causes of delay in discharge from the PACU, unanticipated hospital admission and increase in medical costs.[11–13] The duration of PACU stay was shorter in children who received prophylactic ondansetron and it could have been even shorter, especially in the prophylactic group, had we used criteria based on discharge alone and not fixed the minimum duration of PACU stay at 2 h (which we needed for initial evaluation of outcomes and management). We did not assess another clinically and economically important outcome, the rate of unanticipated hospital admission, as all our patients were inpatients for 24 h. Even if the children had been discharged immediately after surgery, it would have been difficult to compare the incidence of this infrequent event because of our relatively small sample size.[11 12]

In this era of value-conscious health care, the cost of a drug or practice to benefit a patient is a significant factor. Value-based care is essentially the best patient outcome achieved at a reasonable cost.[14 15] This is the first clinical trial that has evaluated the utility of prophylactic *vs* prompt therapeutic use of ondansetron on the basis of value-based care principles.[14 15] Children in the prophylactic ondansetron group had significantly higher parental satisfaction scores than those in the therapeutic group. The lower cost to benefit a child and lower cost per PONV-free child in the prophylactic ondansetron group reassert the value of prophylaxis with ondansetron as a cost-effective modality compared with early symptomatic treatment in high-risk patients. Even though prophylactic ondansetron was a cost-effective approach, the higher cost of ondansetron has been a major concern. Recently, it has been demonstrated that prophylactic dexamethasone administered at induction is cost-effective in managing PONV after paediatric strabismus repair.[16] However, as a sole prophylactic antiemetic, neither dexamethasone nor ondansetron was adequate to eliminate PONV completely in this high-risk population.[16] Scuderi and colleagues have recently shown that multimodal management of PONV decreases the incidence of PONV better than prophylactic ondansetron alone in a population with a high risk of PONV.[17]

For an individual patient, the use of routine prophylactic ondansetron compared with 'wait and treat' may increase the direct drug costs. However, we believe that the 'downstream benefits' (higher patient satisfaction, earlier fast tracking and shorter PACU stay) more than compensated for the additional cost.

References

1 Sadhasivam S, Shende D, Madan R. Prophylactic ondansetron in prevention of postoperative nausea and vomiting following pediatric strabismus surgery: a dose response study. *Anesthesiology* 2000; **92**: 1035–42

2 Fisher DM. The 'big little problem' of postoperative nausea and vomiting: do we know the answer yet? *Anesthesiology* 1997; **87**: 1271–3

3 Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. *N Engl J Med* 1988; **318**: 1728–33

4 Scuderi PE, James RL, Harris L, Mims GR. Antiemetic prophylaxis does not improve outcomes after outpatient surgery when compared to symptomatic treatment. *Anesthesiology* 1999, **90**: 360–71

5 Aldrete JA. The post-anesthesia recovery score revisited *J Clin Anesth* 1995; **7**: 89–91.

6 White PF, Song D. New criteria for fast tracking after outpatient anesthesia: a comparison with the modified Aldrete's scoring system. *Anesth Analg* 1999; **88**: 1069–72

7 Pawar DK. Pain management. In: Brown TCK, Fisk GC, eds. *Anaesthesia for Children*, 2nd edn. Melbourne: Blackwell Scientific Publications, 1992; 127–37

8 Watcha MF, Bras PJ, Cieslak GD, Pennant JH. The dose–response relationship of ondansetron in preventing postoperative emesis in pediatric patients undergoing ambulatory surgery. *Anesthesiology* 1995; **82**: 47–52

9 Watcha MF, White PF. Economics of anesthetic practice. *Anesthesiology* 1997; **86**: 1170–96

British Journal of Anaesthesia **89** (3) 479–85 (2002)

BJA

LABORATORY INVESTIGATIONS

Effects of halothane and isoflurane on the contraction, relaxation and energetics of rat diaphragmatic muscle

B. Bouhemad[1], O. Langeron[1], G. Orliaguet[2], P. Coriat[1] and B. Riou[1,3]*

[1]Laboratory of Experimental Anaesthesiology, Department of Anaesthesiology and Critical Care, CHU Pitié-Salpêtrière, Assitance Publique-Hôpitaux de Paris (AP-HP), Université Pierre et Marie Curie, [2]Department of Anaesthesiology and Critical Care, CHU Necker-Enfants Malades, AP-HP, and [3]Department of Emergency Medicine and Surgery, CHU Pitié-Salpêtrière, AP-HP, Université Pierre et Marie Curie, Paris, France

**Corresponding author: Departement d'Anesthésie-Réanimation, CHU Pitié-Salpêtrière, 47 Boulevard de l'Hôpital, F-75651 Paris Cedex 13, France*

Background. The inotropic effects of halogenated anaesthetics on diaphragmatic muscle remain a matter of debate. Their effects on its relaxation are poorly understood, although diaphragmatic relaxation is recognized as an important physiological process that may interfere with diaphragmatic performance, fatigue and arterial blood flow.

Methods. The effects of halothane and isoflurane (1 or 2× minimum alveolar concentration [1 or 2 MAC]) on contraction and relaxation of rat diaphragm muscle strips (n=40) were studied *in vitro* from force–velocity curves obtained at various loads from isotonic to isometric conditions. From these curves we determined the peak power output and the curvature. Data are mean (SD) percentage of baseline values.

Results. At 1 MAC, isoflurane and halothane induced no significant inotropic and lusitropic effects. At 2 MAC, isoflurane induced a negative inotropic effect (active force, 93(5)% of baseline). Halothane and isoflurane induced a significant decrease in the peak power output at 2 MAC (88(8) and 86(9)% of baseline; P<0.05), without significant changes in the curvature of the force–velocity curve. At 2 MAC isoflurane under high loads and halothane under low loads induced moderate negative lusitropic effects.

Conclusion. Halothane and isoflurane induced very moderate inotropic and lusitropic effects, suggesting that the decrease in diaphragm function observed *in vivo* is not related to a direct effect on diaphragmatic contractility.

Br J Anaesth 2002; **89**: 479–85

Keywords: anaesthetics volatile, halothane; anaesthetics volatile, isoflurane; muscle skeletal, diaphragm; muscle skeletal, contractility

Accepted for publication: May 3, 2002

When anaesthetics are administered during spontaneous breathing, or during recovery from anaesthesia, the respiratory effects of volatile anaesthetics may be of clinical importance, particularly when diaphragmatic function is compromised. The direct effects of halogenated anaesthetics on the intrinsic mechanical properties of the diaphragm remain a matter of debate. These effects are difficult to study *in vivo* because assessment of intrinsic mechanical properties of any muscle requires simultaneous measurements of force, length and velocity,[1] which are difficult to measure simultaneously *in vivo* Even if such measurements could be obtained, interference with arterial blood flow, arterial blood gases, abdominal pressure and thus diaphragmatic load, and neuromuscular transmission would still be difficult to eliminate[2–4] Even *in vitro* studies have provided conflicting results with[5] and without[6] impairment of diaphragmatic contractility by volatile anaesthetics. Although it is well-established that volatile anaesthetics only have modest effects on the contractility of skeletal muscle, their effects have been reported to be more

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

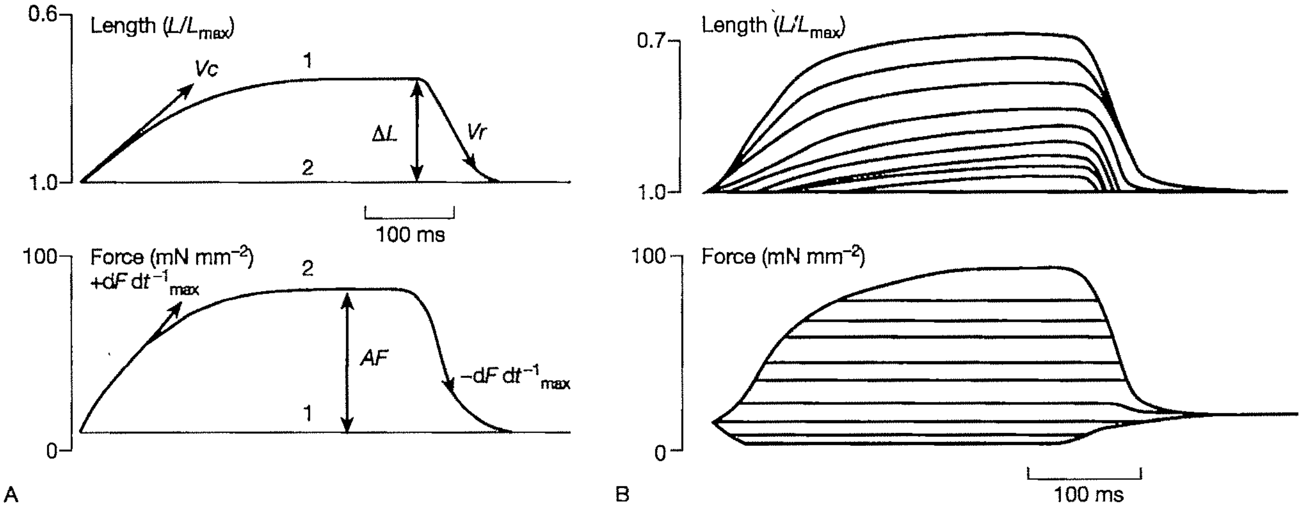


Fig 1 Determination of mechanical variables of contraction and relaxation Muscle shortening length plotted *vs* time (top panels), and force plotted *vs* time (lower panels). (A) Tetanus 1 was isotonic, and tetanus 2 was fully isometric. Shortening (Vc) and lengthening (Vr) velocities, maximal extent of shortening (ΔL), peaks of positive (+dF.dt^{-1}_{max}) and negative (–dF dt^{-1}_{max}) force and active force (AF_{max}) were determined from these typical isotonic and isometric tetanic stimuli. (B) Ten consecutive contractions at different afterload levels from zero load to isometric load. L_{max} is the initial muscle length corresponding to the apex of the length–force curve.

pronounced in the diaphragm.[4] Moreover, although diaphragmatic relaxation is now recognized as an important physiological process that may interfere with diaphragmatic performance, fatigue and arterial blood flow,[7] the effects of halogenated anaesthetics on this function remain poorly understood.

We therefore conducted an *in vitro* study of the effects of halothane and isoflurane on isolated rat diaphragm. The experimental model used enabled us to determine their effects, not only on contraction (inotropy), but also on relaxation (lusitropy) and energetics.[8]

Methods

Animal care conformed to the recommendations of the Helsinki Declaration and the study was performed in accordance with the regulations of the official regulations issued by the French Ministry of Agriculture.

After brief ether anaesthesia, adult Wistar rats (220–260 g) were killed and a muscle strip from the ventral part of the costal diaphragm was carefully dissected from the muscle *in situ*. As previously reported,[9] this diaphragm strip was immediately suspended vertically in a 200-ml jacketed reservoir with Krebs–Henseleit bicarbonate buffer solution (NaCl 118 mM, KCl 4.5 mM, $MgSO_4$ 1.2 mM, KH_2PO_4 1.1 mM, $NaHCO_3$ 25 mM, $CaCl_2$ 2.5 mM, and glucose 4.5 mM) prepared daily with highly purified water. The jacketed reservoir was maintained at 29°C with a thermostatic water circulator and a temperature probe. The bathing solution was bubbled with 95% oxygen–5% carbon dioxide, resulting in a pH of 7.40.

Preparations were field stimulated by means of two platinum electrodes with rectangular pulses of 1 ms duration at a rate of 10 pulses min^{-1} in the twitch mode. Experiments were conducted after a 25-min stabilization period, at the initial muscle length at the apex of the length-active isometric tension curve (L_{max}). Measurements of mechanical parameters were made using tetanic stimulation at 50 Hz (10 trains min^{-1} of 300 ms duration, 1 ms rectangular pulses) to obtain maximal contractions. Cross-sectional area was calculated from the ratio of muscle weight to muscle length, assuming a muscle density of 1.06.

The electromagnetic lever system has been described previously.[10] All analyses were made from digital records of force and length obtained with a computer, as previously described.[8–10] Variables characterizing contraction (Fig. 1A) were the shortening velocity (Vc), extent of shortening (ΔL), peak of the positive force derivative normalized per cross-sectional area (+dF.dt^{-1}) and active force normalized per cross-sectional area (AF). Variables characterizing relaxation (Fig. 1A) were the lengthening velocity (Vr) and peak of the negative force derivative normalized per cross-sectional area (–dF.dt^{-1}). Mechanical variables were calculated from 10 consecutive tetanic contractions preloaded at L_{max} with increasing afterload from zero load to fully isometric contraction (Fig. 1B). The first contraction was abruptly clamped to zero load just after the electrical stimulus, with critical damping in order to slow the first and rapid shortening overshoot resulting from the recoil of series passive elastic components, enabling determination of the maximum unloaded shortening velocity (V_{max}). The second contraction was isotonic and loaded with preload only. The maximum extent of shortening (ΔL_{max}), and the maximum lengthening velocity (Vr_{max}) were determined from this contraction. The last contraction was fully isometric at L_{max}. The maximum active force (AF_{max}) and the peak of the positive (+dF.dt^{-1}_{max}) and negative (–dF.dt^{-1}_{max}) force derivatives were determined from this fully isometric

Table 1 Baseline values of mechanical parameters. ΔL=maximal extent of shortening, V_{max}=maximal unloaded shortening velocity, Vr_{max}=maximal lengthening velocity, AF_{max}=maximal isometric active force normalized per cross-sectional area; $+dF.dt^{-1}{}_{max}$=peak of the positive force derivative normalized per cross-sectional area, $-dF.dt^{-1}{}_{max}$=peak of the negative force derivative normalized per cross-sectional area; E_{max}=peak power output, G=curvature of the force–velocity curve. Data are presented as means (SD). There were no significant differences between groups

Parameters	Control (n=8)	1 MAC halothane (n=8)	2 MAC halothane (n=8)	1 MAC isoflurane (n=8)	2 MAC isoflurane (n=8)
Isotony					
ΔL_{max} ($\%L_{max}$)	25 (6)	23 (2)	28 (2)	26 (6)	27 (4)
V_{max} (L_{max} s^{-1})	4.5 (0.7)	4.5 (0.8)	4.9 (0.7)	4.2 (0.8)	4.9 (0.7)
Vr_{max} (L_{max} s^{-1})	8.4 (1.3)	7.2 (1.2)	8.8 (2.1)	8.2 (0.9)	8.4 (1.1)
$Vr_{max}/\Delta L_{max}$ (L_{max} $s^{-1}.\%L_{max}{}^{-1}$)	0.35 (0.06)	0.32 (0.05)	0.32 (0.07)	0.32 (0.08)	0.32 (0.06)
Isometry					
AF_{max} (mN mm^{-2})	79 (21)	82 (13)	76 (21)	87 (18)	79 (10)
$+dF\ dt^{-1}{}_{max}$ (mN mm^{-2} s^{-1})	970 (262)	1033 (308)	1027 (96)	945 (153)	984 (199)
$-dF\ dt^{-1}{}_{max}$ (mN mm^{-2} s^{-1})	2196 (571)	2113 (395)	2027 (417)	2341 (486)	2298 (424)
Energetics					
E_{max} (L_{max} mN mm^{-2} s^{-1})	53 (12)	49 (12)	52 (10)	50 (15)	48 (9)
G	2.9 (0.9)	2.6 (0.6)	3.0 (0.7)	2.4 (0.5)	3.0 (0.4)

contraction. V_{max} and AF_{max} described the contraction phase (inotropy), while Vr_{max} and $-dF.dt^{-1}{}_{max}$ described the relaxation phase. Nevertheless, since changes in the contraction phase induce co-ordinated changes in the relaxation phase, relaxation parameters alone cannot adequately assess lusitropy, and therefore, variations in contraction and relaxation must be considered simultaneously to quantify drug-induced changes in lusitropy.[9] Thus, we calculated the ratios $Vr_{max}/\Delta L_{max}$ and $-dF.dt^{-1}{}_{max}/AF_{max}$, which assessed lusitropy in isotonic and isometric conditions, respectively. Moreover, relaxation is highly dependent on load level, and thus must also be studied over the entire load continuum (from preload to fully isometric contraction).[7] To characterize the isotonic relaxation process, the relationship between Vr and ΔL was determined over the load continuum.[11] Indeed, ΔL is the main determinant of Vr. The relationship between Vr and ΔL is almost linear up to 80–90% of ΔL_{max}, but then Vr increases to a lesser degree as ΔL increases up to ΔL_{max}. To characterize the isometric relaxation process, the relationship between $-dF.dt^{-1}$ and AF was determined over the load continuum (from 10 to 100% AF_{max}).[12] In muscle isometrically relaxing at initial muscle length, the relationship between $-dF.dt^{-1}$ and AF is almost linear up to 80% of AF_{max}, and then $-dF.dt^{-1}$ decreases to a lesser degree as AF increases up to AF_{max}.

Muscle energetic parameters were determined from Huxley's equations.[13] The force–velocity curve was derived from the peak shortening velocity (Vc) plotted against the total force (TF=resting force+active force) normalized per cross-sectional area.[14] Both measurements were obtained from 10 tetanic contractions, from zero load to fully isometric contraction. The total force–velocity (TF–Vc) curve was fitted according to the Hill equation:[15]

$$(TF+a)(Vc+b)=(TF_{max}+a)b$$

where –a and –b are the asymptotes of the hyperbola, TF_{max} is the calculated maximum isometric total force for Vc=0. The following energetic parameters were derived from the Hill hyperbola: the curvature of the hyperbola (G) and the non-normalized maximum power output (E_{max}).[14] G is linked to myothermal efficiency and cross-bridge kinetics. The more curved the Hill hyperbola (i.e. the higher value of G), the higher the muscle efficiency.[16]

Diaphragmatic strips were divided into five groups (n=8 in each group), as follows: (i) time-matched control, (ii) 1 minimum alveolar concentration (1 MAC) halothane, (iii) 2 MAC halothane, (iv) 1 MAC isoflurane and (v) 2 MAC isoflurane. Halothane and isoflurane were added to the carbon dioxide–oxygen mixture with a specific calibrated vaporizer (Fluotec 3 for halothane and Fortec 3 for isoflurane; Cyprane Ltd., Keighley, UK). The gas mixture bubbled continuously in the bathing solution. To minimize evaporation of volatile anaesthetics, the jacketed reservoir was almost completely sealed with a thin paraffin layer. The concentration of volatile anaesthetics in the gas phase was continuously monitored with a calibrated infrared analyser (Artema MM 206 SD; Taema, Antony, France). The halothane concentrations used were 0.6 and 1.2%, and isoflurane concentrations were 0.8 and 1.6%. These concentrations are equivalent to 1 and 2 MAC of halothane and isoflurane, respectively, in the adult rat at 29°C.[17] Halothane and isoflurane were administered for a 15-min equilibration period before measurements were made.

Data are expressed as mean (SD). Comparisons of two means were performed using the Student's t test and comparison of several means was performed using analysis of variance and Newman–Keuls test. The energetic parameters were derived from the Hill equation[15] using multilinear regression and the least-square method, as previously described.[14] All P-values were two-tailed, and a P-value <0.05 was considered significant.

Results

Mean cross-sectional area was 1.07 (0.25) mm^2, and mean L_{max} was 8.7 (1.0) mm. The baseline values of mechanical

Table 2 Effects of halothane and isoflurane on diaphragmatic muscle ΔL=maximal extent of shortening; V_{max}=maximal unloaded shortening velocity, Vr_{max}=maximal lengthening velocity; AF_{max}=maximal isometric active force normalized per cross-sectional area; $+dF\,dt^{-1}_{max}$=peak of the positive force derivative normalized per cross-sectional area, $-dF\,dt^{-1}_{max}$=peak of the negative force derivative normalized per cross-sectional area; E_{max}=peak power output, G=curvature of the force–velocity curve Data are mean percentage of baseline values (SD) $^*P<0.05$ *vs* control group

Parameter	Control (n=8)	1 MAC halothane (n=8)	2 MAC halothane (n=8)	1 MAC isoflurane (n=8)	2 MAC isoflurane (n=8)
Isotony					
ΔL_{max}	99 (2)	97 (5)	101 (4)	101 (2)	100 (3)
V_{max}	95 (5)	99 (4)	97 (4)	98 (3)	96 (6)
Vr_{max}	92 (4)	89 (7)	84 (10)	94 (6)	92 (4)
$Vr_{max}/\Delta L_{max}$	92 (4)	91 (4)	83 (10)*	94 (6)	93 (4)
Isometry					
AF_{max}	105 (7)	100 (6)	97 (8)	100 (5)	93 (5)*
$+dF\,dt^{-1}_{max}$	99 (8)	98 (9)	91 (9)	101 (9)	91 (10)*
$-dF\,dt^{-1}_{max}$	100 (7)	98 (9)	90 (11)	93 (6)	83 (4)*
$-dF\,dt^{-1}_{max}/AF_{max}$	95 (10)	98 (7)	92 (6)	94 (4)	90 (2)*
Energetics					
E_{max}	99 (6)	99 (9)	88 (8)*	99 (11)	86 (9)*
G	101 (7)	103 (17)	100 (12)	107 (15)	106 (19)

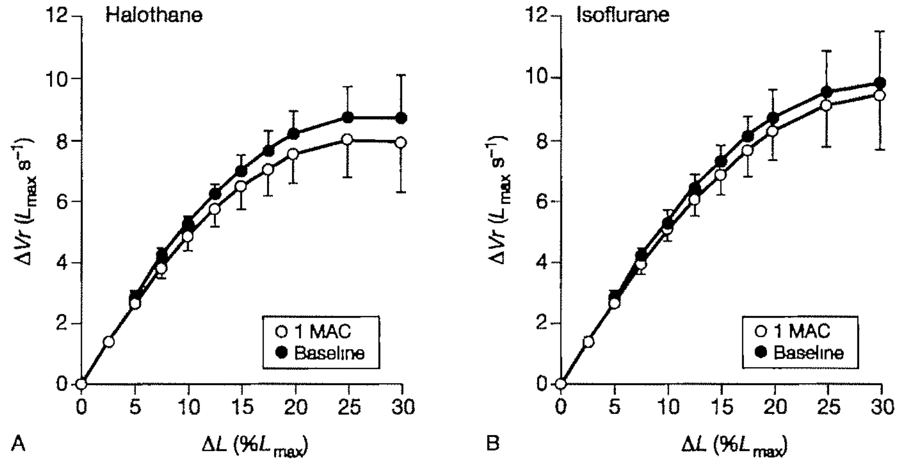


Fig 2 Effects of (A) 1 MAC halothane (n=8) and (B) 1 MAC isoflurane (n=8) on the relationship between lengthening velocity (Vr) and extent of shortening (ΔL) in diaphragmatic muscles. ΔL is the main determinant of Vr, and the initial part of $Vr/\Delta L$ relationship is almost linear up to 80–90% of ΔL_{max}; then Vr increases to a lesser degree as ΔL increases up to ΔL_{max}. Data are means (SD).

and energetic parameters were not significantly different between groups (Table 1).

Under low load (V_{max}, ΔL, Vr_{max}) at 1 and 2 MAC, halothane and isoflurane induced no significant inotropic or lusitropic effects (Table 2). Under high load, isoflurane at 2 MAC induced significant negative inotropic (AF_{max}) and lusitropic ($-dF.dt^{-1}_{max}$) effects (Table 2). Conversely, at 1 MAC, halothane and isoflurane induced no significant effects.

Isoflurane induced no significant changes in the $Vr_{max}/\Delta L_{max}$ ratio (Table 2). Halothane 2 MAC induced a significant decrease of the $Vr_{max}/\Delta L_{max}$ ratio. Because ΔL is the main determinant of Vr, we also studied the relationship, $Vr/\Delta L$, over the load continuum. Halothane and isoflurane did not significantly modify the initial linear part of the $Vr/\Delta L$ relationship (Fig. 2). Isoflurane at 2 MAC induced a significant change in the $-dF.dt^{-1}_{max}/AF_{max}$ ratio. Because AF is the main determinant of $-dF.dt^{-1}$, we also studied the relationship $-dF.dt^{-1}/AF$ over the load continuum. Under baseline conditions, an increase in load accelerated $-dF.dt^{-1}$ in a linear manner of up to around 80% of AF_{max}. However, under high loading conditions, $-dF.dt^{-1}$ decreased as AF increased. Halothane and isoflurane did not significantly modify the initial linear part of the $-dF.dt^{-1}/AF$ relationship (Fig. 3).

The force–velocity curves were correctly depicted by the Hill hyperbola, as shown by the high correlation coefficients (0.998 (0.002)). Halothane and isoflurane at 2 MAC induced a moderate but significant decrease in E_{max} (Table 2). Halothane and isoflurane did not significantly modify the curvature, G, of the force–velocity curve (Table 2, Fig. 4).

Discussion

The main findings of this study were that (i) at 2 MAC, isoflurane under high loads (isometric conditions) induced a

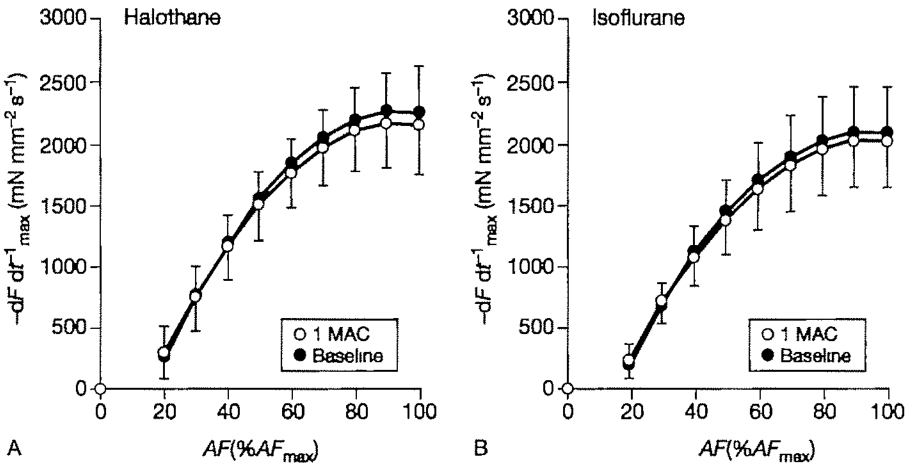


Fig 3 Effects of (A) 1 MAC halothane (n=8) and (B) 1 MAC isoflurane (n=8) on the relationship between the peak of the negative force derivative ($-dF\ dt^{-1}$) and active force (AF) in diaphragmatic muscles. AF is the main determinant of Vr; and the initial part of $-dF.dt^{-1}/AF$ relationship is almost linear up to 80–90% of AF_{max}; then $-dF\ dt^{-1}$ decreases to a lesser degree as AF increases up to AF_{max}. Data are means (SD).

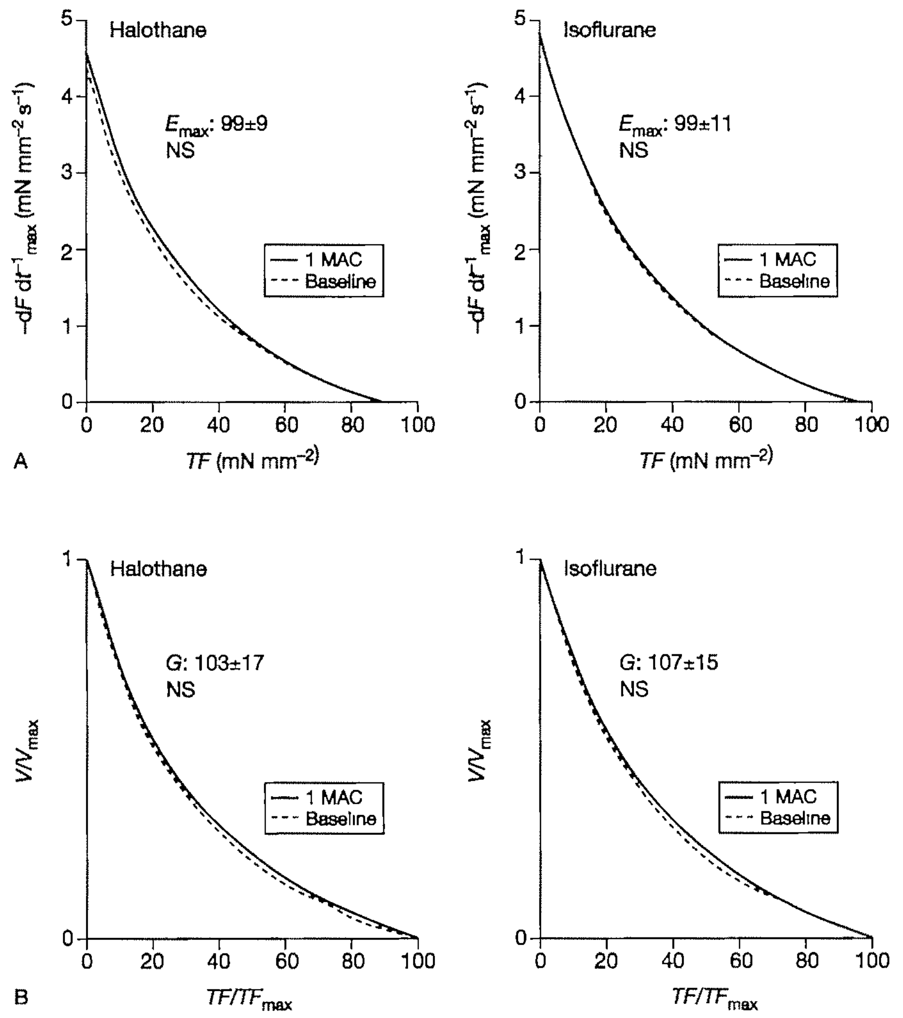


Fig 4 Effects of 1 MAC of halothane (n=8) and isoflurane (n=8) on (A) the total force (F)–velocity (V) relationship and (B) the normalized F–V relationship. E_{max}=maximum power output, G=curvature of the F–V curve; NS=not significant

negative inotropic effect; (ii) at 2 MAC, isoflurane under high loads and halothane under low loads (isotonic conditions) induced a negative lusitropic effect; (iii) halothane and isoflurane at 2 MAC decreased the maximal power output, E_{max}, whereas they did not modify the curvature, G, of the force–velocity curve.

In vitro, halogenated anaesthetics have a moderate positive inotropic effect on skeletal muscle,[18] but the diaphragm, unlike other skeletal muscles, requires extracellular calcium for its normal contractile function.[19] Conflicting effects of volatile anaesthetics have been observed in *in vivo* experiments. Indeed some studies have suggested that halogenated anaesthetics induce diaphragmatic contractile dysfunction,[4 20 21] whereas other studies did not.[6 22] Because of the anaesthetic-induced changes in arterial blood pressure and diaphragmatic blood flow, central nervous system and neuromuscular transmission, the precise effects of halogenated anaesthetics on intrinsic diaphragmatic contraction are very difficult to assess *in vivo*. In an *in vitro* study under isometric conditions, Kawaga and colleagues[5] have suggested that halothane and sevoflurane decrease the force of the hamster diaphragm only during fatigue. In our study in isolated rat diaphragm, we confirmed the lack of significant effect of halothane under isometric conditions. When the effects of anaesthetics on myocardial muscle are compared as force development (isometric condition) *vs* shortening (isotonic condition), anaesthetics typically depress force development more than velocity of shortening.[23] Our study agrees with these results because we found a moderate negative inotropic effect only under isometric, and not isotonic, conditions.

In our study, halothane and isoflurane at 2 MAC decreased the maximal power output, E_{max}, whereas they did not modify the curvature, G, of the force–velocity curve (Table 3). G is linked to myothermal economy and cross-bridge kinetics.[14 16] The more curved the hyperbola (i.e. the higher value of G), the higher the muscle efficiency. It has been shown that fatigue increases mechanical efficiency in rat diaphragm.[24] Rat diaphragm is composed of both faster fatigue-sensitive and slower fatigue-resistant fibre types, and fatigue displaces the characteristics of the muscle towards the slower fatigue-resistant fibres.[24] In our study, halothane and isoflurane did not modify the G curvature and these findings support a lack of effect of volatile anaesthetics on fast fatigue-sensitive fibres.[25]

In skeletal muscle, relaxation consists of an isotonic lengthening, during which the muscle returns to its initial length (isotonic relaxation), and thereafter an isometric decay, during which the muscle returns to its initial resting force (isometric relaxation).[26] In separately studying isotonic and isometric relaxation, the experimental model used in the present study enabled determination of the effects of halogenated anaesthetics on the main subcellular pathways responsible for relaxation. In striated muscle, sarcomere length modulates myofilament calcium sensitivity and thus relaxation. Under isotonic conditions, which correspond to significant sarcomere shortening, the sensitivity of troponin C to calcium is low and relaxation proceeds more rapidly than contraction, apparently due to rapid calcium uptake by the sarcoplasmic reticulum.[11] Only halothane at 2 MAC induced a significant decrease in the $Vr_{max}/\Delta L_{max}$ ratio, suggesting an increase in resting cytosolic calcium using halothane. Isometric relaxation was studied by the $-dF.dt^{-1}/AF$ relationship. The initial part of this relationship up to 80% of AF_{max} is determined by passive mechanisms,[12] including the effects of external load and restoring forces, and was not altered by halothane or isoflurane (Fig. 3). Under isometric (i.e. high load) conditions, which correspond to greater sarcomere length, the affinity of troponin C to calcium is higher, and relaxation is mainly determined by the dissociation of calcium from troponin C, rather than calcium uptake by the sarcoplasmic reticulum.[11] Isoflurane at 2 MAC induced a significant change in the $-dF.dt^{-1}{}_{max}/AF_{max}$ ratio, suggesting an interaction with contractile proteins. Our results agree with the effects observed on the myocardial and skeletal muscles because we found (1) an impairment of isotonic relaxation by halothane, supporting a greater effect of halothane on calcium leakage from the sarcoplasmic reticulum[27] and a higher resting cytosolic calcium; (2) an impairment of isometric relaxation by isoflurane as recently showed by Kunst and colleagues[28] on skeletal muscle, supporting a greater interaction between contractile proteins and isoflurane than halothane.[29]

The assessment of the effects of halogenated anaesthetics on isometric and isotonic relaxation was not only motivated by the study of main intracellular components involved in relaxation, i.e. sarcoplasmic reticulum and calcium myofilament sensitivity. Indeed, relaxation of the diaphragm is now recognized as an important active physiological process that requires energy and whose alteration may produce clinically relevant consequences.[7] An incomplete relaxation prevents the return of the diaphragm to its optimal length between each inspiration (i.e. at the apex of the length–active isometric tension curve) and thus optimal force generation. Secondly, during extreme activity, blood flow to the diaphragm is reduced or even abolished during contraction, so relaxation is critical to allow adequate blood flow.[30] Very few studies have assessed the effects of halogenated anaesthetics on diaphragmatic relaxation. Veber and colleagues[22] reported a prolonged relaxation rate with isoflurane (1.5 MAC) in the rat, but relaxation was studied only in quasi-isometric conditions and not on the load continuum.[7] Moreover, the effects on relaxation were not assessed by taking into account the simultaneous effects of contraction.[7 9] In our study, we observed that halogenated anaesthetics weakly interfere with diaphragmatic relaxation, and only at a high concentration (2 MAC) not usually encountered during spontaneous ventilation in anaesthetized patients.

The following points must be considered when assessing the relevance of our results. First, because this study was conducted *in vitro*, it dealt only with intrinsic diaphragmatic contractility. Observed changes in diaphragmatic function after anaesthetic administration may also depend on modifications in diaphragmatic arterial blood flow, central nervous system respiratory drive, modification of diaphragmatic shape and neuromuscular transmission. Second, the study was conducted at 29°C because the stability of the model is low at 37°C. In addition, the temperature had to be lowered to prevent core hypoxia.[31]

In conclusion, in isolated rat diaphragmatic muscle, halothane and isoflurane induced very moderate inotropic and lusitropic effects, which were only significant at 2 MAC, and myothermal efficiency was not significantly affected. These results suggest that the decrease in diaphragm function observed *in vivo* with halogenated anaesthetics is not related to a direct effect on diaphragmatic contractility.

References

1 Brutsaert DL, Sonnenblick EH. Force velocity–length–time relations of the contractile elements in heart muscle of the cat. *Circ Res* 1969; **24**: 137–49

2 Clergue F, Viires N, Lemesle P, Aubier M, Viars P, Pariente R. Effect of halothane on diaphragmatic muscle function in pentobarbital-anesthetized dogs. *Anesthesiology* 1986; **64**: 181–7

3 Drummond GB. Does halothane really reduce diaphragmatic contractility? *Anesthesiology* 1986; **65**: 701–2

4 Dureuil B, Viires N, Nivoche Y, *et al.* Different effects of halothane on diaphragm and hindlimb muscle in rats. *J Appl Physiol* 1987; **63**: 1757–62

5 Kagawa T, Maekawa N, Mikawa K, Nishina K, Yaku H, Obara H The effect of halothane and sevoflurane on fatigue-induced changes in hamster diaphragmatic contractility. *Anesth Analg* 1998; **86**: 392–7

6 Kochi T, Ide T, Mizuguchi T, Nishino T. Halothane does not depress contractile function of fresh or fatigued diaphragm in pentobarbitone-anaesthetized dogs. *Br J Anaesth* 1992, **68**: 562–6

7 Coirault C, Chemla D, Lecarpentier Y. Relaxation of diaphragm muscle. *J Appl Physiol* 1999, **87**: 1243–52

8 Coirault C, Riou B, Bard M, Suard I, Lecarpentier Y. Contraction, relaxation, and economy of force generation in isolated human diaphragm muscle. *Am J Respir Crit Care Med* 1995; **152**: 1275–83

9 Orliaguet G, Langeron O, Coirault C, Fratea S, Coriat P, Riou B. Effects of dantrolene on rat diaphragm muscle during postnatal maturation. *Anesthesiology* 2001; **94**: 468–74

10 Lecarpentier YC, Chuck LHS, Housmans PR, De Clerck NM, Brutsaert DL Nature of load dependence of relaxation in cardiac muscle. *Am J Physiol* 1979; **237**: H455–60

11 Coirault C, Chemla D, Pery-Man N, Suard I, Lecarpentier Y. Mechanical determinants of isotonic relaxation in the isolated diaphragm muscle. *J Appl Physiol* 1993; **75**: 2265–72

12 Coirault C, Chemla D, Pery-Man N, Suard I, Salmeron S, Lecarpentier Y. Isometric relaxation of isolated diaphragm muscle: influence of load, length, time, and stimulation. *J Appl Physiol* 1994; **76**: 1468–75

13 Huxley AF. Muscle structure and theories of contraction. *Prog Biophys Chem* 1957; **7**: 255–318

14 Lecarpentier Y, Chemla D, Blanc FX, *et al.* Mechanics, energetics, and crossbridge kinetics of rabbit diaphragm during congestive heart failure. *FASEB J* 1998; **12**: 981–9

15 Hill AV. The efficiency of mechanical power development during muscular shortening and its relation to load *Proc R Soc Biol (Lond)* 1964; **159**: 319–24

16 Alpert NR, Mulieri L. Increased myothermal economy of isometric force generation in compensated cardiac hypertrophy induced by pulmonary artery constriction in the rabbit. A characterization of heat liberation in normal and hypertrophied right ventricular papillary muscles *Circ Res* 1982, **50**: 491–500

17 Vitez TS, White PF, Eger EI. Effects of hypothermia on halothane MAC and isoflurane MAC in the rat. *Anesthesiology* 1974; **41** 80–1

18 Su JY, Bell JG. Intracellular mechanism of action of isoflurane and halothane on striated muscle of the rabbit. *Anesth Analg* 1986, **65**: 457–62

19 Zavecz JH, Anderson WM. Role of extracellular Ca^{2+} in diaphragmatic contraction: effects of ouabain, monensin, and ryanodine *J Appl Physiol* 1992; **73**: 30–5

20 Ide T, Kochi T, Isono S, Mizuguchi T. Effect of sevoflurane on diaphragmatic contractility in dogs. *Anesth Analg* 1992; **74** 739–46

21 Kochi T, Ide T, Isono S, Mizuguchi T, Nishino T. Different effects of halothane and enflurane on diaphragmatic contractility *in vivo* *Anesth Analg* 1990; **70**: 362–8

22 Veber B, Dureuil B, Viires N, Aubier M, Pariente R, Desmonts JM. Effects of isoflurane on contractile properties of diaphragm *Anesthesiology* 1989; **70** 684–8

23 Housmans PR. Negative inotropy of halogenated anesthetics in ferret ventricular myocardium. *Am J Physiol* 1990; **259**: H827–34

24 Coirault C, Chemla D, Pery-Man N, Suard I, Lecarpentier Y Effects of fatigue on force–velocity relation of diaphragm. Energetic implications. *Am J Respir Crit Care Med* 1995, **151**: 123–8

25 Tavernier BM, Haddad E, Adnet PJ, Etchrivi TS, Lacroix D, Reyford H. Isoform-dependent effects of halothane in human skinned striated fibers. *Anesthesiology* 1996; **84**: 1138–47

26 Jewell BR, Wilkie DR. The mechanical properties of relaxing muscle. *J Physiol (Lond)* 1960; **152**: 30–47

27 Nelson TE, Sweo T. Ca^{2+} uptake and Ca^{2+} release by skeletal muscle sarcoplasmic reticulum. Differing sensitivity to inhalational anesthetics. *Anesthesiology* 1988; **59**. 571–7

28 Kunst G, Graf BM, Schreiner R, Martin E, Fink RHA. Differential effects of sevoflurane, isoflurane, and halothane on Ca^{2+} release from the sarcoplasmic reticulum of skeletal muscle. *Anesthesiology* 1999; **91**: 179–86

29 Bosnjak ZJ, Aggarwal A, Turner LA, Kampine JM, Kampine JP Differential effects of halothane, enflurane, and isoflurane on Ca^{2+} transients and papillary muscle tension in guinea pigs *Anesthesiology* 1992; **76**. 123–31

30 Hussain SN. Regulation of ventilatory muscle blood flow *J Appl Physiol* 1996; **81**. 1455–68

31 Paradise NF, Schmitter JL, Surmitis JM. Criteria for adequate oxygenation of isometric kitten papillary muscles. *Am J Physiol* 1981; **241**: H348–53

British Journal of Anaesthesia 89 (3) 486–91 (2002)

Pharmacological preconditioning: comparison of desflurane, sevoflurane, isoflurane and halothane in rabbit myocardium†

V. Piriou[1*], P. Chiari[1], F. Lhuillier[1], O. Bastien[1], J. Loufoua[2], O. Raisky[1], J. S. David[1], M. Ovize[2] and J.-J. Lehot[1]

[1]Service d'Anesthésie Réanimation and [2]Laboratoire de physiologie Lyon Nord,
Hôpital cardio-vasculaire Louis Pradel, Avenue Doyen Lépine, F-69500 Lyon Bron, France
**Corresponding author*

Background. Recent investigations showed that isoflurane can induce pharmacological preconditioning. The present study aimed to compare the potency of four different halogenated anaesthetics to induce preconditioning.

Methods. Anaesthetized open-chest rabbits underwent 30 min of coronary artery occlusion followed by 3 h of reperfusion. Before this, rabbits were randomized into one of five groups and underwent a treatment period consisting of either no intervention for 45 min (control; n=10), or 30 min of 1 MAC halogenated anaesthetic inhalation followed by 15 min of washout. End-tidal concentrations of halogenated agents were 3.7% for sevoflurane (n=11), 1.4% for halothane (n=9), 2.0% for isoflurane (n=11), and 8.9% for desflurane (n=11). Area at risk and infarct size were assessed by blue dye injection and tetrazolium chloride staining.

Results. Mean (SD) infarct size was 54 (18)% of the risk area in untreated controls and 40 (18)% in the sevoflurane group (P>0.05, ns). In contrast, mean infarct size was significantly smaller in the halothane, isoflurane, and desflurane groups: 26 (18)%, 32 (18)% and 16 (17)%, respectively (P<0.05 vs control).

Conclusions. Halothane, isoflurane and desflurane induced pharmacological preconditioning, whereas sevoflurane had no significant effect. In this preparation, desflurane was the most effective agent at preconditioning the myocardium against ischaemia.

Br J Anaesth 2002; **89**: 486–91

Keywords: anaesthetics volatile; heart, myocardial function

Accepted for publication: April 30, 2002

There is growing evidence that halogenated anaesthetics are cardioprotective. They decrease infarct size following a prolonged ischaemic insult[1–3] and improve postischaemic functional recovery (i.e. myocardial stunning).[4–6] Preconditioning is an endogenous phenomenon whereby repeated brief episodes of coronary artery occlusion protect the heart against further sustained ischaemia.[7 8] Recent studies have demonstrated that administration of some pharmacological agents, including halogenated anaesthetics, before prolonged ischaemia can precondition the heart ('pharmacological preconditioning').[9 10] In 1997, Cope and colleagues,[9] using a Langendorff rabbit model, Kersten and colleagues[10] and Cason and colleagues,[11] using dog and rabbit *in vivo* models, reported that the pre-administration of isoflurane followed by a washout period preconditioned the heart. Later studies have used isoflurane to investigate the underlying mechanisms of this protection.[12–14] Activation of mitochondrial K_{ATP} channels is probably involved in isoflurane-induced preconditioning.[14] Halothane has been shown to induce pharmacological preconditioning in an *in vitro* model.[9] Four different inhalational anaesthetic agents are currently used in our clinical practice: halothane, isoflurane, sevoflurane and desflurane. However, whether their myocardial preconditioning potency is equivalent is unknown. The aim of the present study was therefore to compare the efficacy of these four halogenated agents at triggering pharmacological preconditioning in the *in vivo* rabbit model.

---

†This work was presented at the 23rd annual meeting of the Society of Cardiovascular Anesthesiologists, Vancouver, Canada, May 2001 (*Anesth Analg* 2001; 92: SCA39)

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

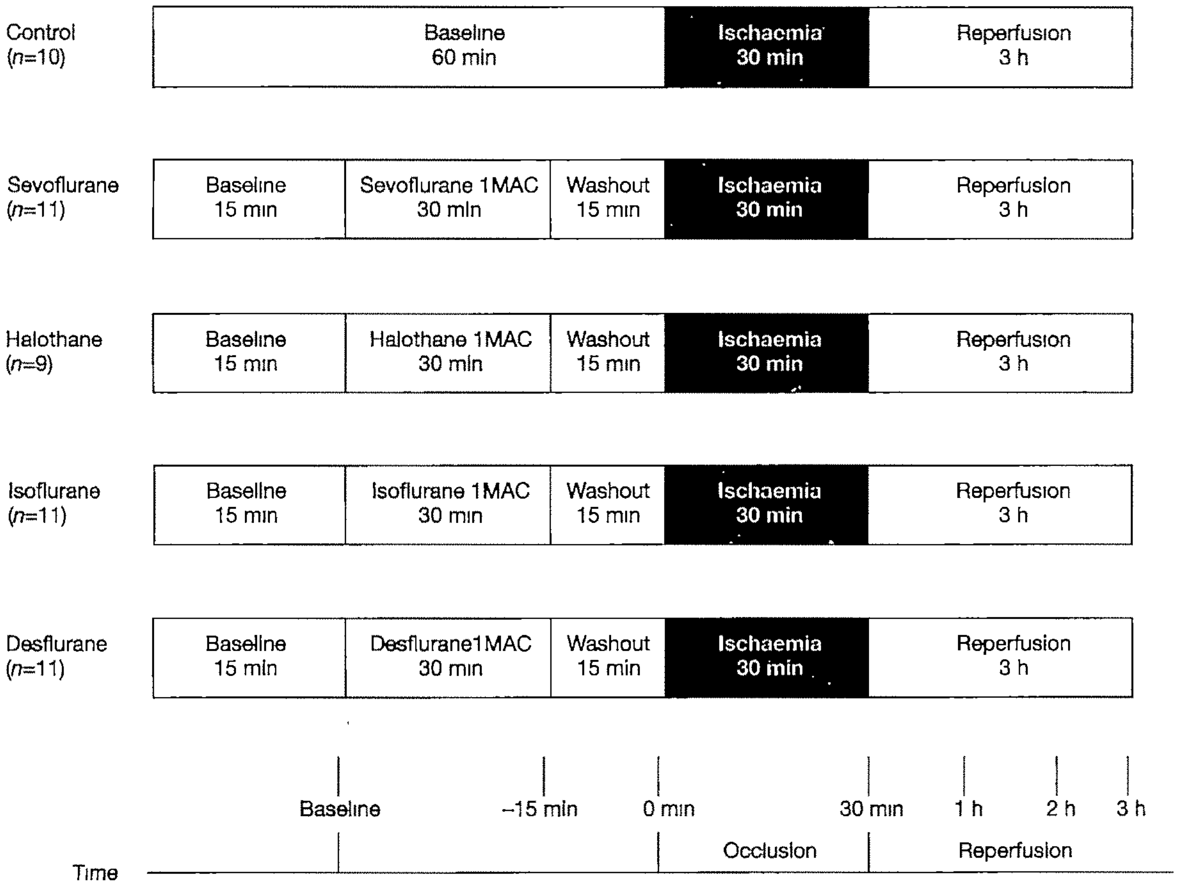


Fig 1 Experimental protocol Filled bars represent ischaemia; empty bars represent perfusion. Sevoflurane, halothane, isoflurane and desflurane were titrated to end-tidal concentrations of 3.7%, 1.4%, 2.0% and 8.9%, respectively.

Material and methods

All experiments performed in this study conformed to the *Guiding Principles in the Care and Use of Animals* approved by the American Physiologic Society. The Laboratoire de Physiologie Lyon Nord and the investigators had authorization from the French government to perform such animal studies.

A total of 73 New Zealand White rabbits of either sex (2.0–2.5 kg) were premedicated with xylazine 5 mg kg^{-1} i.m. and anaesthetized with ketamine hydrochloride 50 mg kg^{-1} i.m. Anaesthesia was maintained by continuous infusion of a mixture of ketamine 3 mg kg^{-1} h^{-1} and xylazine 1.5 mg kg^{-1} h^{-1}. Adequate depth of anaesthesia was ensured before any surgical procedures by the absence of pedal and palpebral reflexes. Following tracheostomy, the animal's lungs were ventilated mechanically (Servo ventilator 900B, Siemens-Elema, Sweden and SA2 ventilator, Drager, Lübeck, Germany) with 100% oxygen. Tidal volume was set at 15 ml kg^{-1} and the respiratory rate to 35 bpm. Ventilation was adjusted to maintain end-tidal CO$_2$ E'_{CO_2} in the physiological range. End-tidal gas concentrations were measured continuously (gas analyser Capnomac Ultima, Datex, Helsinki, Finland). Body temperature, recorded through a thermistor inserted into the oesophagus, was maintained between 39.0 and 40.5°C by means of a servo-controlled heating element incorporated into the operating table. Limb lead II of the ECG was monitored continuously by means of subcutaneous needle electrodes. Systemic arterial pressure was monitored using a Gould pressure transducer connected to a 1-mm fluid-filled catheter inserted in the right carotid artery. The right internal jugular vein was catheterized with a 1 mm catheter to infuse fluids and drugs. Hetastarch 5 ml kg^{-1} h^{-1} was infused continuously via this intravenous cannula. Fentanyl 50 µg i.v. was injected before thoracotomy to provide adequate analgesia.

The heart was exposed via a left thoracotomy The first large marginal branch of the circumflex artery was identified and a 5/0 Dexon suture was passed around this artery, approximately halfway between the apex and the base. The suture ends were threaded through a small vinyl tube to make a snare to perform further coronary occlusion and reperfusion. After the surgical procedure, a 15-min stabilization period was allowed.

In all groups, the coronary artery was occluded for 30 min. Myocardial ischaemia was confirmed by the appearance of a regional cyanosis on the epicardium distal to the snare, akinesia or bulging in this area, and a marked ST segment

Table 1 Haemodynamic measurements in different experimental groups Data are mean (SD). *$P<0.05$ *vs* control

	Control	Sevoflurane	Halothane	Isoflurane	Desflurane
Systolic arterial pressure (mm Hg)					
Baseline	81 (16)	75 (14)	80 (16)	78 (13)	78 (14)
–15 min occlusion	80 (20)	56 (18)*	60 (9)	62 (5)	54 (8)*
Pre-occlusion	77 (19)	80 (17)	77 (20)	73 (14)	81 (10)
30 min occlusion	71 (11)	68 (11)	69 (14)	66 (14)	74 (12)
1 h reperfusion	71 (13)	62 (25)	76 (11)	65 (16)	78 (9)
2 h reperfusion	68 (15)	71 (10)	72 (13)	65 (11)	77 (11)
3 h reperfusion	67 (19)	69 (10)	66 (19)	67 (18)	70 (15)
Heart rate (beats min^{-1})					
Baseline	191 (36)	175 (25)	177 (32)	188 (16)	191 (26)
–15 min occlusion	198 (39)	163 (34)	215 (48)	191 (28)	201 (30)
Pre-occlusion	203 (38)	172 (29)	181 (39)	194 (28)	184 (25)
30 min occlusion	210 (37)	171 (28)	175 (27)	204 (39)	175 (29)
1 h reperfusion	212 (24)	167 (33)*	171 (56)	192 (39)	177 (29)
2 h reperfusion	211 (27)	168 (25)*	157 (25)*	197 (46)	174 (19)
3 h reperfusion	212 (31)	176 (15)	163 (43)*	179 (44)	172 (29)

elevation on the ECG. After 30 min, the snare was released and reperfusion allowed for a period of 3 h. Reperfusion was visually confirmed by the appearance of hyperaemia. The thread passed around the marginal artery was left in place.

At the end of the reperfusion period, the coronary artery was briefly re-occluded and diluted Uniperse blue (Ciba-Geigy, Hawthorne, NY, USA) was injected into the jugular vein to delineate the *in vivo* area at risk. With this technique, the previously non-ischaemic area appears blue whereas the area at risk remains unstained. Anaesthetized rabbits were then injected with potassium chloride (1 g) and the heart was excised and cut into five or six 2-mm-thick transverse slices.

After removing right ventricular tissue, each slice was weighed and identified. The basal surface of each slice was photographed for future measurement of the area at risk. Each slice was then incubated for 15 min in tetrazolium chloride to differentiate infarcted (pale) from viable (red) myocardial area.[15] Each slice was then photographed again. Using enlarged projections, the boundaries of the different areas on each slice were traced. The extent of left ventricle (LV) area, area at risk and infarct size were quantified by computerized planimetry (ImageJ software, version 1.01z, National Institutes of Health, USA) and corrected for the weight of the tissue slice. Total weights of area at risk and area of necrosis were then calculated and expressed as weight (g) or as percentages of total LV weight. It was decided prospectively that hearts with a risk region <10% of the LV weight would be excluded from the study.

Experimental groups

Animals were randomly assigned into five groups (Fig. 1). All groups underwent a 30-min coronary artery occlusion and 3 h of reperfusion. Before this prolonged ischaemia, they underwent a 45-min treatment period. After the 15-min stabilization period, the halogenated anaesthetic was added to the inspired gas for 30 min and discontinued 15 min before ischaemia. Volatile anaesthetics were titrated to an end-tidal concentration of 3.7% sevoflurane, 1.4% halothane, 2.0% isoflurane and 8.9% desflurane, corresponding to 1.0 MAC of each anaesthetic in the rabbit.[16–18] For each animal, end-tidal concentration of halogenated agent was less than 0.1% at the end of the washout period.

Isoflurane and sevoflurane were purchased from Abbott laboratories (Queenborough, UK), halothane from Zeneca Pharma (Cergy, France) and desflurane from Baxter (Lessines, Belgium).

Statistics

Statistical analysis of haemodynamics and E'_{CO_2} was performed using two-way ANOVA with repeated measures on one factor. LV weight and area at risk were analysed by analysis of variance. Effect of pretreatment on percent of risk zone infarcted was analysed by one-way analysis of variance followed by Dunnett's post test when appropriate. Differences in infarct sizes among groups were evaluated by analysis of covariance and post-hoc least significance difference test, with infarct size as the dependent variable and area at risk as the covariant. Statistical calculations were performed using Statistica 5.0 (Statsoft Inc., Tulsa, OK, USA) and GraphPad InStat version 3.00 for Windows 95 (GraphPad Software, San Diego, CA, USA). All values are expressed as mean (SD). $P<0.05$ was considered significant.

Results

Mortality and exclusion

Of the 73 rabbits included in this study, seven were excluded because of fatal ventricular fibrillation during coronary occlusion (one control, one sevoflurane, one halothane, two isoflurane and two desflurane) and six

Table 2 Area at risk, infarct size and risk zone infarcted Data are mean (SD). LV, left ventricle. *$P<0$ 05 *vs* control

	Control	Sevoflurane	Halothane	Isoflurane	Desflurane
LV weight (g)	2 93 (0.62)	2.69 (0.35)	2 60 (0 26)	2.74 (0.37)	2 79 (0 49)
Area at risk (% LV)	30 (10)	41 (12)	47 (13)	38 (12)	36 (13)
Area at risk (g)	0 92 (0.31)	1 11 (0 34)	1.21 (0.33)	1.01 (0 28)	0 99 (0 32)
Infarct size (g)	0.51 (0.25)	0.47 (0 29)	0.29 (0 18)*	0 33 (0 23)*	0 14 (0 12)*
Risk zone infarcted (%)	54 (18)	40 (18)	26 (18)*	32 (18)*	16 (17)*

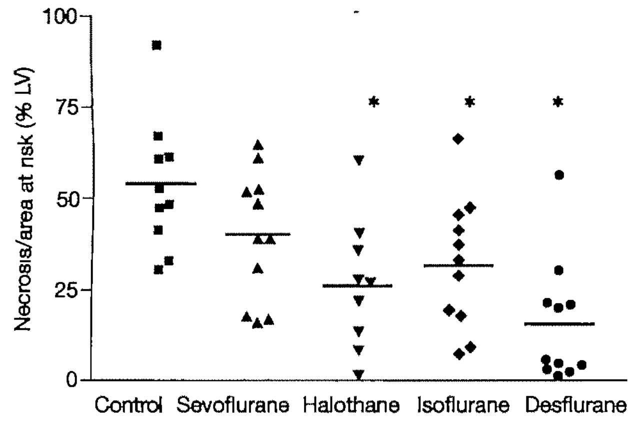


Fig 2 Infarct size expressed as percentage of area at risk for each individual animal. Horizontal lines are means Halothane, isoflurane and desflurane pre-administration significantly reduced infarct size, sevoflurane pre-administration had no effect *$P<0$ 05 *vs* control.

because of severe heart failure (obvious cardiac dilatation and systolic arterial pressure <40 mm Hg) during coronary occlusion or reperfusion (one control, two sevoflurane, one halothane, one isoflurane and one desflurane). Seven rabbits were excluded because of technical problems during surgical preparation and one because the photograph of the heart slices was unreadable. Data are presented for the 52 remaining rabbits: 10 control and 11 sevoflurane-, 9 halothane-, 11 isoflurane- and 11 desflurane-treated rabbits.

Haemodynamic data

Haemodynamic data, including heart rate and arterial pressure, are summarized in Table 1. Inhalational anaesthetic administration decreased systolic arterial pressure consistently but transiently in all groups. This effect was statistically significant for the sevoflurane and desflurane groups. E'_{CO_2} and body temperature did not differ between the groups.

Infarct size

Data for the area at risk and infarct size are presented in Table 2 and Figure 2. LV weight and area at risk were comparable between the different groups, with mean value of area at risk ranging from 30 (10)% to 47 (13)% of LV weight.

Infarct size in the control group was 54 (18)% of the area at risk. Pretreatment with sevoflurane failed to significantly decrease infarct size (40 (18)% of area at risk) whereas pre-administration of halothane, isoflurane or desflurane significantly attenuated myocardial infarct size (26 (18)%, 32 (18)% and 16 (17)% of area at risk, respectively).

These data were confirmed when comparing the weights of the infarct size with area at risk as a covariant, which represents a major determinant of myocardial infarction in the rabbit model (Table 2).

Discussion

The present study showed that a 30-min pre-administration of halothane, isoflurane or desflurane, followed by a 15-min washout period, significantly decreased myocardial infarct size following a subsequent prolonged ischaemic insult. Desflurane was the most potent agent. Sevoflurane had no significant effect in this model.

Several studies have reported the cardioprotective effects of halogenated anaesthetics against ischaemia-reperfusion, depending on the timing of administration and the ischaemic time. Warltier and colleagues[4] and Meissner and colleagues[5] showed that halothane, isoflurane and desflurane can attenuate myocardial stunning. All four inhalational anaesthetics can limit infarct size in *in vivo* preparations, whether they have been administered during a sustained ischaemia or during the reperfusion. When given during a sustained ischaemic period, halothane[1] and isoflurane[2] decreased infarct size. When given only during the reperfusion period, desflurane and sevoflurane limited myocardial necrosis, whereas isoflurane had no effect.[19] A 30-min inhalation of sevoflurane[3] or desflurane[20] discontinued just before the onset of ischaemia also had significant anti-necrotic effect.

Pre-administration of isoflurane also exerted a protective effect by reducing infarct size when the discontinuation of this volatile agent was followed by a washout period before ischaemia. This isoflurane-induced pharmacological preconditioning has been shown *in vitro*[9] and *in vivo*.[10 11] Similar observations have been made using halothane and enflurane.[9] Similar to ischaemic preconditioning, isoflurane-induced preconditioning involves adenosine receptors,[12] G_i protein[13] and mitochondrial K_{ATP} channels.[14] Adenosine A1 receptors and protein kinase C can also modulate halothane-induced preconditioning.[9]

Our study is the first to address the issue of the intensity of the preconditioning effect of these four halogenated agents in the same experimental conditions. We found that the degree of protection differed between the four agents. Sevoflurane failed to significantly reduce infarct size. While halothane and isoflurane appeared very similar, desflurane displayed the most potent cardioprotective effect. Consistent findings have been reported by Toller and colleagues using a canine model.[3] The authors showed that discontinuation of a 30-min administration of 1 MAC sevoflurane just before onset of ischaemia decreased infarct size. However, when sevoflurane was discontinued 30 min before ischaemia, the myocardial protective effect disappeared. Two-minute ischaemic preconditioning was not long enough to precondition the heart. However, 2-min ischaemia associated with a 30-min sevoflurane pre-administration and a 30-min washout period decreased infarct size. Preconditioning induced by desflurane has not been shown previously. As with ischaemic preconditioning and isoflurane-induced preconditioning, K_{ATP} channels may be responsible for desflurane cardioprotection.[20]

The reasons for the differences between the four inhalational agents remain unclear. Hypotension induced by volatile agents does not seem to be involved in the volatile-anaesthetic-induced preconditioning, the main mechanism involved being a direct effect on K_{ATP} channels.[10] In the current study, desflurane and sevoflurane were the most hypotensive agents, with opposite effects on infarct size. This is in agreement with Cope and colleagues,[9] who showed a lack of correlation between infarct size and the hypotensive effects of volatile anaesthetics. Although +dp/dt and –dp/dt were not measured, it is possible that the different lusitropic and inotropic effects of the four anaesthetics might influence these results.

The basal anaesthetic protocol might influence our results, because ketamine has been shown to block preconditioning[21] whereas δ opiates such as fentanyl confer cardioprotection by mimicking ischaemic preconditioning.[22] However, all groups received the same anaesthetic protocol, and it is unlikely that this could explain the differences between groups.

Like ischaemic preconditioning,[23] some volatile anaesthetics, such as halothane and isoflurane, can inhibit apoptosis.[24] Although we did not measure tissue ATP concentrations or assess apoptosis, we cannot rule out that sevoflurane pre-administration can be protective by decreasing apoptosis without significantly decreasing infarct size.

One possible explanation of the most pronounced effect of desflurane in our study is an increase in sympathetic activity[25] or the release of myocardial catecholamines[26] induced by this agent. Indeed, it has been shown that α-adrenergic agonists may trigger ischaemic preconditioning.[27 28] Regarding an increase in sympathetic activity, desflurane-induced hypotension was not concomitant of tachycardia in the present study, which might signify a lack of sympathetic activation. Moreover, Pac-Soo and colleagues[29] showed in a rabbit model that although low concentrations of isoflurane (1.2%) and desflurane (6%) increased renal sympathetic nerve activity, higher concentrations (such as those used in our study) depressed sympathetic activity. On the other hand, Gueugniaud and colleagues suggested that desflurane may be responsible for myocardial catecholamine release in isolated rat myocardium.[26] However, it is not known how myocardial catecholamine release may influence desflurane-induced preconditioning.

Toller and colleagues[3] suggested that the lack of effect of sevoflurane might be explained by the low blood gas solubility coefficient (0.62),[30] resulting in less residual drug in the myocardium at the end of the washout period than with isoflurane. This does not fit with our data, however, since we demonstrated that desflurane, with the lowest blood–gas partition coefficient (0.49),[30] exhibited the most pronounced effect.

We only examined the effects of 1 MAC; however, we cannot rule out that there is a dose–response curve and that a higher concentration of sevoflurane might be effective in preconditioning the rabbit heart.

In conclusion, our results indicate that halothane, isoflurane and desflurane, but possibly not sevoflurane, can induce pharmacological preconditioning. Further studies are needed to address the selective efficacy and mechanism of action for each of these agents.

Acknowledgements

This study was supported in part by the Department of Anaesthesiology and Intensive Care, Association pour la Recherche Cardio-Vasculaire, Pr JJ Lehot, Hopital cardio-vasculaire et Pneumologique Louis Pradel, Lyon, France and by the Fondation de France, Bourse de recherche Bullukian (Champagne au Mont d'Or, France). A special acknowledgement is due to our laboratory technician, Florence Arnal

References

1 Davis RF, DeBoer LW, Rude RE, *et al.* The effect of halothane anesthesia on myocardial necrosis, hemodynamic performance, and regional myocardial blood flow in dogs following coronary artery occlusion. *Anesthesiology* 1983; **59**: 402–11

2 Davis RF, Sidi A. Effect of isoflurane on the extent of myocardial necrosis and on systemic hemodynamics, regional myocardial blood flow, and regional myocardial metabolism in dogs after coronary artery occlusion. *Anesth Analg* 1989; **69**: 575–86

3 Toller WG, Kersten JR, Pagel PS, *et al.* Sevoflurane reduces myocardial infarct size and decreases the time threshold for ischaemic preconditioning in dogs. *Anesthesiology* 1999; **91**: 1437–46

4 Warltier DC, al Wathiqui MH, Kampine JP, Schmeling WT. Recovery of contractile function of stunned myocardium in chronically instrumented dogs is enhanced by halothane or isoflurane. *Anesthesiology* 1988; **69**: 552–65

5 Meissner A, Weber TP, Van Aken H, *et al.* Recovery from myocardial stunning is faster with desflurane compared with propofol in chronically instrumented dogs. *Anesth Analg* 2000; **91**. 1333–8

6 Kersten JR, Lowe D, Hettrick DA, *et al.* Glyburide, a K_{ATP}

channel antagonist, attenuates the cardioprotective effects of isoflurane in stunned myocardium. *Anesth Analg* 1996; **83**: 27–33

7 Murry CE, Jennings RB, Reimer KA. Preconditioning with ischaemia: a delay of lethal cell injury in ischaemic myocardium. *Circulation* 1986; **74**: 1124–36

8 Reimer KA, Murry CE, Yamasawa I, *et al.* Four brief periods of myocardial ischaemia cause no cumulative ATP loss or necrosis. *Am J Physiol* 1986; **251**: H1306–15

9 Cope DK, Impastato WK, Cohen MV, Downey JM. Volatile anaesthetics protect the ischaemic rabbit myocardium from infarction. *Anesthesiology* 1997; **86**: 699–709

10 Kersten JR, Schmeling TJ, Pagel PS, *et al.* Isoflurane mimics ischaemic preconditioning via activation of K(ATP) channels: reduction of myocardial infarct size with an acute memory phase *Anesthesiology* 1997; **87**: 361–70

11 Cason BA, Gamperl AK, Slocum RE, Hickey RF Anesthetic-induced preconditioning: previous administration of isoflurane decreases myocardial infarct size in rabbits. *Anesthesiology* 1997; **87**: 1182–90

12 Ismaeil MS, Tkachenko I, Gamperl AK, *et al.* Mechanisms of isoflurane-induced myocardial preconditioning in rabbits. *Anesthesiology* 1999; **90**: 812–21

13 Toller WG, Kersten JR, Gross ER, *et al.* Isoflurane preconditions myocardium against infarction via activation of inhibitory guanine nucleotide binding proteins. *Anesthesiology* 2000; **92**. 1400–7

14 Piriou V, Chiari P, Knezynski S, *et al.* Prevention of isoflurane-induced preconditioning by 5-hydroxydecanoate and gadolinium: possible involvement of mitochondrial adenosine triphosphate-sensitive potassium and stretch-activated channels. *Anesthesiology* 2000, **93**: 756–64

15 Vivaldi MT, Kloner RA, Schoen FJ. Triphenyltetrazolium staining of irreversible ischaemic injury following coronary artery occlusion in rats. *Am J Pathol* 1985; **121**: 522–30

16 Drummond JC. MAC for halothane, enflurane, and isoflurane in the New Zealand white rabbit: and a test for the validity of MAC determinations. *Anesthesiology* 1985; **62**: 336–8

17 Scheller MS, Saidman LJ, Partridge BL. MAC of sevoflurane in humans and the New Zealand white rabbit. *Can J Anaesth* 1988; **35**: 153–6

18 Doorley BM, Waters SJ, Terrell RC, Robinson JL. MAC of I-653 in beagle dogs and New Zealand white rabbits. *Anesthesiology* 1988; **69**: 89–91

19 Preckel B, Schlack W, Comfère T *et al.* Effects of enflurane, sevoflurane, and desflurane on reperfusion injury after regional myocardial ischaemia in the rabbit heart *in vivo*. *Br J Anaesth* 1998, **81**: 905–12

20 Toller WG, Gross ER, Kersten JR, *et al.* Sarcolemmal and mitochondrial adenosine triphosphate-dependent potassium channels: mechanism of desflurane-induced cardioprotection. *Anesthesiology* 2000; **92**: 1731–9

21 Mullenheim J, Frassdorf J, Preckel B, Thamer V, Schlack W. Ketamine, but not S(+)-ketamine, blocks ischemic preconditioning in rabbit hearts in vivo *Anesthesiology* 2001; **94**: 630–6

22 Schultz JE, Hsu AK, Gross GJ Morphine mimics the cardioprotective effect of ischemic preconditioning via a glibenclamide-sensitive mechanism in the rat heart. *Circ Res* 1996; **78**: 1100–4

23 Piot CA, Padmanaban D, Ursell PC, Sievers RE, Wolfe CL. Ischemic preconditioning decreases apoptosis in rat hearts in vivo. *Circulation* 1997; **96**. 1598–604

24 Zaugg M, Jamali NZ, Lucchinetti E, Shafiq SA, Siddiqui MA. Norepinephrine-induced apoptosis is inhibited in adult rat ventricular myocytes exposed to volatile anesthetics. *Anesthesiology* 2000; **93**: 209–18

25 Ebert TJ, Muzi M. Sympathetic activation with desflurane in humans. *Adv Pharmacol* 1994; **31**: 369–78

26 Gueugniaud PY, Hanouz JL, Vivien B, *et al.* Effects of desflurane in rat myocardium. *Anesthesiology* 1997, **87**: 121–31

27 Tsuchida A, Liu Y, Liu GS, *et al.* Alpha 1-adrenergic agonists precondition rabbit ischaemic myocardium independent of adenosine by direct activation of protein kinase C. *Circ Res* 1994; **75**; 576–85

28 Bankwala Z, Hale SL, Kloner RA. Alpha-adrenoceptor stimulation with exogenous norepinephrine or release of endogenous catecholamines mimics ischaemic preconditioning *Circulation* 1994; **90**. 1023–8

29 Pac-Soo CK, Wang C, Chakrabarti MK, Whitwam JG. Comparison of the effects of inhalational anaesthetic agents on sympathetic activity in rabbits. *Eur J Anaesthesiol* 2000, **17**: 311–8

30 Yasuda N, Eger EI, Weiskopf RB, *et al.* Solubility of desflurane (I-653), sevoflurane, isoflurane, and halothane in human blood. *Masui* 1991; **40**: 1059–62

British Journal of Anaesthesia **89** (3): 492–8 (2002)

Role of propofol and its solvent, intralipid, in nitric oxide-induced peripheral vasodilatation in dogs

M.-F. Doursout[1], P. M. Joseph[1], Y. Y. Liang[1], C. J. Hartley[2] and J. E. Chelly[1*]

[1]*Department of Anesthesiology, The University of Texas–Houston Medical School, 6431 Fannin, MSB 5.020 Houston, TX 77030-1503, USA.* [2]*Department of Internal Medicine, Baylor College of Medicine, Houston, Texas, USA*

**Corresponding author*

Background. The commercial propofol preparation in an intralipid solution causes marked vasodilatation. Both propofol and its solvent seem to stimulate the nitric oxide (NO) pathway. The role of intralipid in cardiac and regional haemodynamic changes induced by propofol and their respective interactions with the NO pathway was assessed.

Methods. Dogs were instrumented to record arterial pressure, heart rate, cardiac output, dP/dt (the first derivative of left ventricular pressure) and vertebral, carotid, coronary, mesenteric, hepatic, portal and renal blood flows. Experimental groups were as follows. Group 1 (control; *n*=11): N-methyl-L-arginine (L-NMA) 20 mg kg^{-1} i.v.; Group 2 (*n*=8): propofol (10 mg ml^{-1}) 4 mg kg^{-1} i.v. bolus followed by 0.6 mg kg^{-1} min^{-1}; Group 3 (*n*=6): intralipid 0.25 ml kg^{-1} bolus followed by 0.06 ml kg^{-1} min^{-1}. After 60 min, L-NMA was injected in Groups 2 and 3.

Results. Propofol induced increases in heart rate, coronary and carotid blood flows, and decreases in systemic vascular resistance and dP/dt. Intralipid increased renal blood flow, carotid vascular resistance and mesenteric vascular resistance. In the presence of intralipid, L-NMA-induced pressor response and systemic, carotid and renal vasoconstriction were more pronounced than in control dogs.

Conclusions. Except for the coronary and carotid circulations, intralipid modulates the NO pathway in cardiac and regional blood flow.

Br J Anaesth 2002; **89**: 492–8

Keywords: blood, haemodynamics; arteries, vasodilators; anaesthetics i.v., propofol

Accepted for publication: April 30, 2002

It is well established that intravenous injection of propofol produces hypotension and peripheral vasodilatation. The mechanism of its cardiovascular effects appears to be complex and is only partially understood even after more than 15 years of research. Pagel and colleagues[1] demonstrated that propofol produces a direct negative inotropic effect that contributes to its cardiovascular properties. Lowe and colleagues[2] demonstrated that the effects of propofol on cardiac function are also indirect and are mediated in part by an increase in aortic compliance and a decrease in systemic vascular resistance. Several mechanisms have been proposed to account for the vasodilatator properties of propofol, such as inhibition of the sympathetic vasoconstrictor nerve activity,[3 4] blockade of calcium channels,[5] activation of K^+_{ATP} channels and stimulation of nitric oxide (NO) production.[6 7]

Propofol, which is mostly lipid soluble, is available in an intralipid solution. Although Hageman and colleagues reported that intralipid itself produced pulmonary vasodilatation,[8] the cardiac and regional haemodynamic properties of intralipid remained unknown in *in vivo* studies. Furthermore, studies performed *in vitro* demonstrated that lipid solutions also modulate endothelial NO activity[9 10] and/or endothelium-dependent relaxation.[11 12] Therefore, we postulated that the propofol solvent, intralipid, may also contribute to the cardiac and regional haemodynamic properties of propofol solution as well as to the propofol-mediated stimulation of the NO pathway.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Materials and methods

The University of Texas Animal Welfare Committee approved this protocol.

Cardiovascular instrumentation

A description of the basic model has been published previously.[13] Briefly, mongrel dogs of either sex, heartworm free, weighing 25–34 kg, were instrumented with catheters in the iliac artery, left atrium and pulmonary artery. A precalibrated ultrasonic flow probe was positioned around the pulmonary artery and a miniature pressure transducer was inserted into the left ventricle. Pulsed Doppler flow probes were positioned around the vertebral, carotid, coronary, mesenteric, hepatic and renal arteries and the portal vein. All transducer leads and catheters were tunnelled subcutaneously to the dorsum of the neck and secured after the thoracotomy was closed. Analgesia and antibiotic prophylaxis were initiated before surgery and maintained thereafter.

Measurements

A detailed description of the measurement techniques has also been published previously.[13–15] Phasic and mean arterial pressure (MAP), pulmonary arterial pressure (PAP), first derivative of left ventricular pressure (dP/dt), heart rate (HR), cardiac output (CO), and carotid, vertebral, coronary, mesenteric, hepatic, portal and renal blood flow (BF) were recorded continuously on a 16-channel Gould brush polygraph. Systemic vascular resistance (SVR) and pulmonary vascular resistance (VR) were calculated as the ratio of MAP or PAP to CO; regional VR was calculated as the ratio of MAP to regional BF.

Experimental design

Dogs were carefully nursed through the first 24 h after surgery, and on subsequent days were trained to lie quietly on the laboratory floor. The dogs were studied no less than 10 days after surgery, when haematocrit was >30% and body temperature, appetite and general appearance were normal. Body weight, body temperature, arterial blood gases and haematocrit were measured before each experiment. All experiments were conducted in fasted conscious dogs lying on their right sides.

Since propofol is mostly lipid soluble, we studied the cardiac and regional haemodynamic properties of propofol and its solvent, intralipid, infused under the same experimental conditions. Furthermore, to determine the role played by intralipid in the propofol-mediated stimulation of NO, we also studied the effects of *N*-methyl-L-arginine (L-NMA), a non-specific inhibitor of NO synthase (NOS), on the cardiac and regional changes produced by propofol and intralipid. Accordingly, animals were randomly distributed into three groups. Animals in Group 1 (n=11, control group) received L-NMA 20 mg kg^{-1} i.v. through a filter (Nalgene™) over 1 min. This dose was chosen because it produced maximum haemodynamic changes in conscious dogs.[16] Animals in Group 2 (n=8) received propofol (10 mg ml^{-1}) 4 mg kg^{-1} i.v. bolus followed by 0.6 mg kg^{-1} min^{-1} for 180 min. Animals in Group 3 (n=6) received intralipid 0.25 ml kg^{-1} bolus followed by 0.06 ml kg^{-1} min^{-1} for 180 min. After 60 min, animals in Groups 2 and 3 received L-NMA 20 mg kg^{-1} i.v. over 1 min. A mixture of nitrogen and oxygen was used to maintain arterial oxygen tension at approximately the same level as in control dogs. Blood gases were monitored every 30 min. Haemodynamic parameters were recorded before and during propofol and intralipid infusions and for 2 h after L-NMA administration.

Table 1 Haemodynamic effects of propofol (n=8) and its solvent intralipid (n=6) recorded at baseline and 60 min (before L-NMA infusion) on haemodynamic parameters dP/dt, the first derivative of left ventricular pressure Data are mean (SEM). BF=blood flow, VR=vascular resistance *P<0 05 *vs* baseline

Measurement	Group	Baseline	60 min
Mean arterial pressure (mm Hg)	Intralipid	100 (5)	105 (7)
	Propofol	95 (6)	88 (8)
Heart rate (beats min^{-1})	Intralipid	86 (4)	90 (5)
	Propofol	89 (4)	121 (7)*
Cardiac output (litres min^{-1})	Intralipid	2 3 (0 50	2 1 (0 4)
	Propofol	1 75 (0 2)	1.8 (0 2)
dP/dt (mm Hg s^{-1})	Intralipid	3163 (196)	3334 (232)
	Propofol	3174 (268)	2622 (272)*
Systemic VR (dyne s^{-1} cm^{-5})	Intralipid	56 (7)	57 (7)
	Propofol	64 (7)	51 (4)*
Carotid BF (ml min^{-1})	Intralipid	115 (10)	104 (10)
	Propofol	137 (22)	167 (26)*
Carotid VR (dyne s^{-1} cm^{-5})	Intralipid	0.96 (0 16)	1.12 (0 15)*
	Propofol	0 73 (0 10)	0 61 (0.08)
Coronary BF (ml min^{-1})	Intralipid	52 (8)	54 (11)
	Propofol	48 (6)	66 (10)*
Coronary VR (dyne s^{-1} cm^{-5})	Intralipid	2.3 (0 4)	2 6 (0 6)
	Propofol	2.2 (0 3)	1 6 (0 2)
Portal BF (ml min^{-1})	Intralipid	379 2 (42)	405 (52)
	Propofol	387 (55)	360 (65)
Portal VR (dyne s^{-1} cm^{-5})	Intralipid	0.28 (0.03)	0 27 (0 03)
	Propofol	0.28 (0 04)	0.27 (0 03)
Hepatic BF (ml min^{-1})	Intralipid	69 (24)	127 (25)
	Propofol	96 (16)	108 (19)
Hepatic VR (dyne s^{-1} cm^{-5})	Intralipid	1.25 (0 2)	1 08 (0.22)
	Propofol	1.5 (0 4)	1.0 (0 3)
Renal BF (ml min^{-1})	Intralipid	89 (11)	102 (11)*
	Propofol	123 (34)	121 (29)
Renal VR (dyne s^{-1} cm^{-5})	Intralipid	1.4 (0 24)	1 2 (0 17)
	Propofol	1.4 (0 48)	0 9 (0 2)
Vertebral BF (ml min^{-1})	Intralipid	19 (2 5)	19 (1.8)
	Propofol	19 (4)	24 7 (7 6)
Vertebral VR (dyne s^{-1} cm^{-5})	Intralipid	5 9 (0 7)	6.0 (0.7)
	Propofol	7 (2)	5 6 (1 4)
Mesenteric BF (ml min^{-1})	Intralipid	99 (7)	93 (7)
	Propofol	117 (30)	103 (26)
Mesenteric VR (dyne s^{-1} cm^{-5})	Intralipid	0 96 (0.03)	1 18 (0 11)*
	Propofol	1 0 (0 2)	1 0 (0.2)
Pulmonary artery pressure (mm Hg)	Intralipid	9 (3)	10 (3)
	Propofol	15 (2)	18 (3)

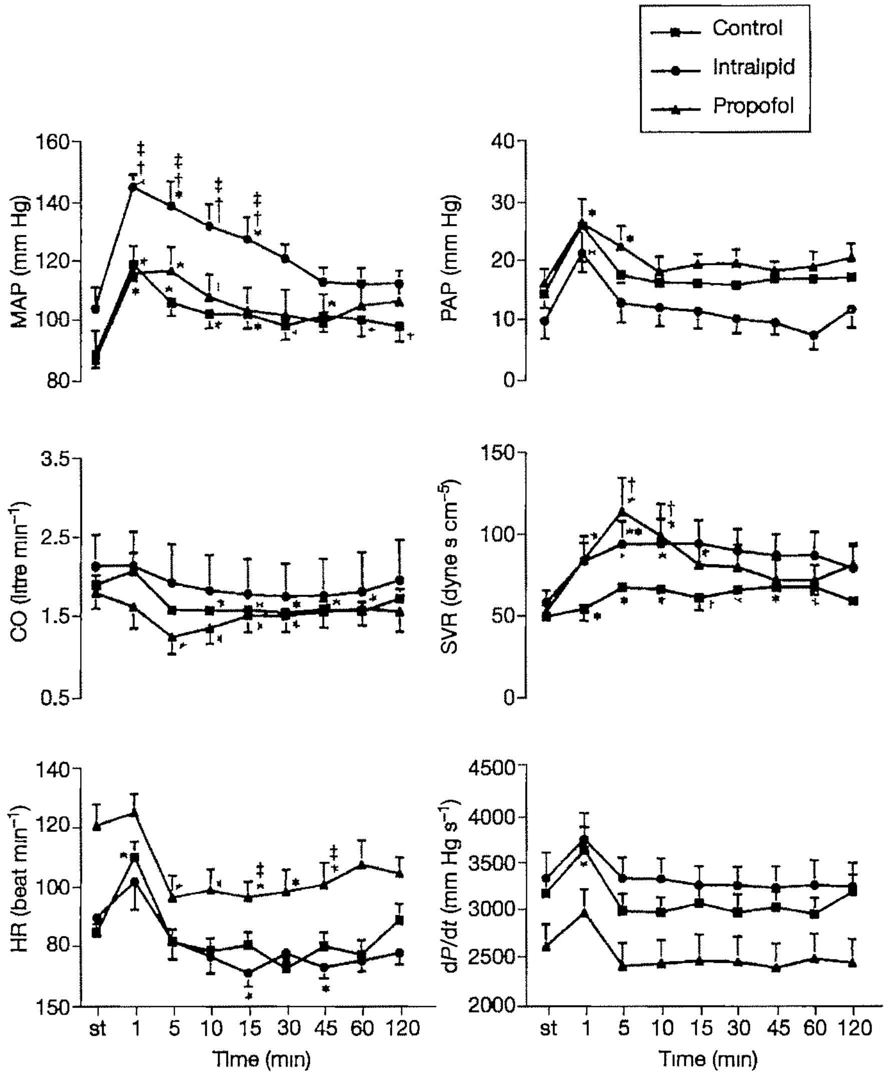


Fig 1 Effects of nitric oxide synthase inhibition using *N*-methyl-L-arginine (L-NMA) in awake dogs (n=11) and during propofol infusion (n= 8) and during intralipid (n=6) infusion on mean arterial blood pressure (MAP), cardiac output (CO), heart rate (HR), pulmonary arterial blood pressure (PAP), systemic vascular resistance (SVR) and dP/dt Data are mean (SEM) *P<0 05 *vs* steady state; **P<0 05 intralipid *vs* awake; †P<0 05 propofol *vs* awake, ‡P<0.05 intralipid *vs* propofol

Data analysis

A paired t-test was performed to analyse the differences between baseline (before drug administration) and steady state (60 min after propofol and/or intralipid). Data obtained in control conditions and under propofol and intralipid were analysed using an analysis of variance (ANOVA) for repeated measures in each group. When differences were significant, multiple within-group comparisons to the steady-state value obtained before L-NMA injections were performed using Fisher's t-test. In addition, when differences between control and propofol and/or intralipid at 60 min were significant, the magnitude of changes produced by L-NMA of each experimental condition was compared using an unpaired t-test. P<0.05 was considered significant. Data are presented as mean (SEM).

Results

Cardiac and regional haemodynamic values before propofol and intralipid administration are presented in Table 1. Baseline values were consistent with those previously reported for trained and unstressed animals and were not significantly different between groups.[13] Changes in cardiac and regional haemodynamic parameters after propofol and intralipid administrations in the presence and absence of L-NMA are presented in Figures 1–4.

Haemodynamic effects of propofol in an intralipid solution, and its solvent, intralipid

As shown in Table 1, continuous infusion of propofol at 4 mg kg^{-1}, followed by 0.6 mg kg^{-1} min^{-1} over 60 min,

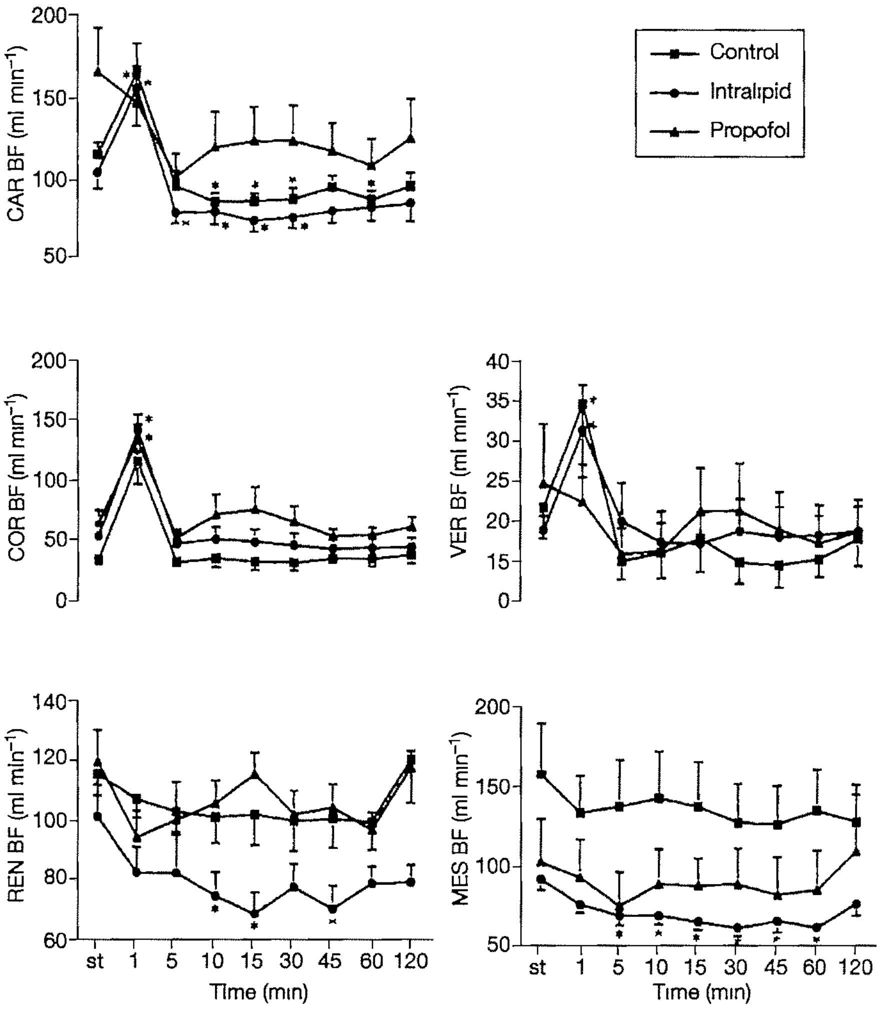


Fig 2 Effects of nitric oxide synthase inhibition using *N*-methyl-L-arginine (L-NMA) in awake dogs ($n=11$) and during propofol infusion ($n=8$) and during intralipid ($n=6$) infusion on carotid (CAR), coronary (COR), renal (REN), vertebral (VER) and mesenteric (MES) blood flow (BF) Data are mean (SEM) $^*P<0.05$ *vs* steady state

induced increases in HR and coronary BF and carotid BF and significant decreases in SVR and dP/dt. In contrast, intralipid increased renal BF and carotid and mesenteric VR.

Effects of NOS inhibition using L-NMA on propofol- and intralipid-induced haemodynamic changes

Effects of L-NMA in control animals

Systemic and regional haemodynamic parameters are presented in Figures 1–4. In Group 1, L-NMA induced brief transient increases in HR and dP/dt. It also produced an immediate and sustained increase in MAP and a decrease in CO, which resulted in an immediate and sustained systemic vasoconstriction. L-NMA also induced brief transient increases in carotid, coronary and vertebral BF. The transient increase in carotid BF was followed by a secondary decrease which lasted 60 min. Hepatic BF decreased at 5 min. Carotid and renal VR increased at 1 and 5 min, respectively, and remained elevated for 60 min, whereas Hep VR increased at 1 and 5 min only. Coronary VR decreased transiently at 1 min.

Effects of propofol in an intralipid solution on NOS inhibition-induced haemodynamic changes

In the presence of propofol and when compared with control experimental conditions, L-NMA produced a decrease in HR at 5–45 min and a more pronounced systemic vasoconstriction that lasted 10 min. The L-NMA-induced increases in carotid and vertebral BF and secondary decreases in carotid and vertebral were abolished. Finally, in these experimental conditions, L-NMA produced a brief secondary coronary vasoconstriction but no renal vasoconstriction.

Effects of intralipid on haemodynamic changes induced by NOS inhibition

In the presence of intralipid and when compared with control experimental conditions, L-NMA produced more

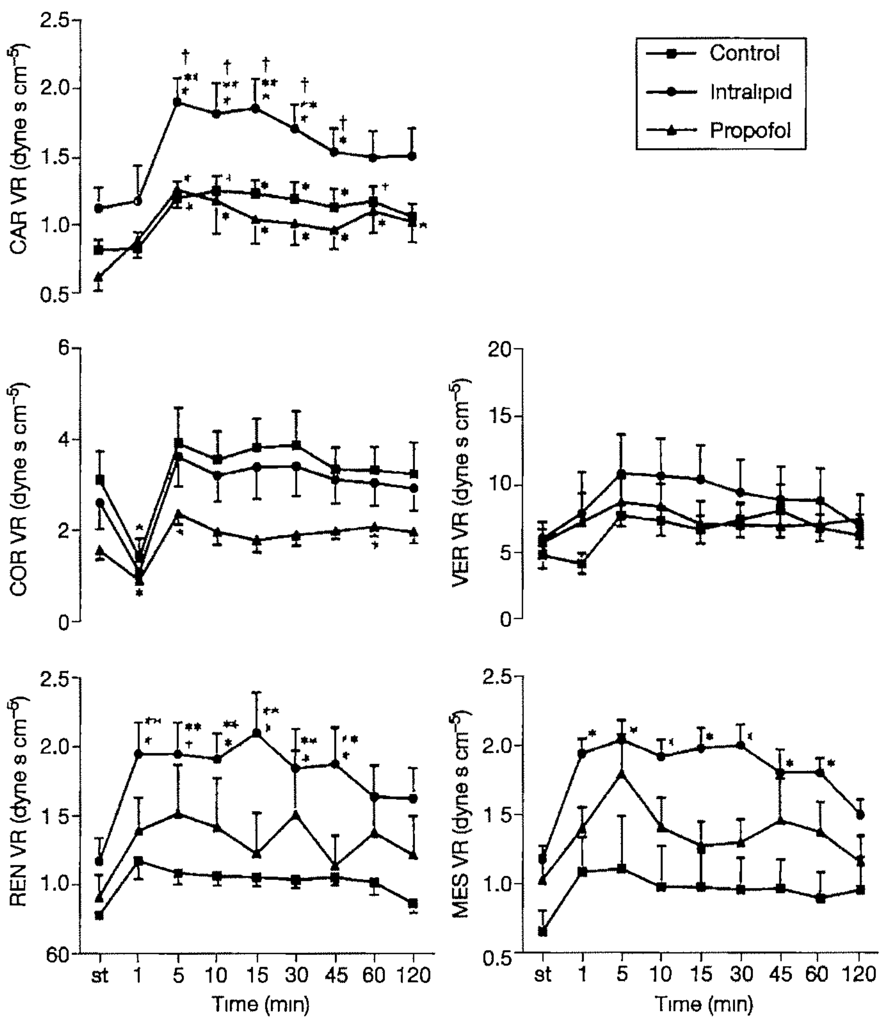


Fig 3 Effects of nitric oxide synthase inhibition using *N*-methyl-L-arginine (L-NMA) in awake dogs (n=11) and during propofol infusion (n=8) and during intralipid (n=6) infusion on carotid (CAR), coronary (COR), renal (REN), vertebral (VER) and mesenteric (MES) vascular resistance (VR). Data are mean (SEM). *P<0.05 *vs* steady state; **P<0.05 intralipid *vs* awake; †P<0.05 propofol *vs* awake.

pronounced increases in MAP and SVR, and carotid vasoconstriction. No decreases in CO or increases in dP/dt were recorded. L-NMA also decreased HR at 15 and 45 min. L-NMA produced sustained decreases in renal BF at 10, 15 and 45 min and in mesenteric BF at 5–60 min, and more pronounced vasoconstriction in the carotid vasculature at 5–45 min, renal vasculature at 1–45 min and mesenteric vasculature at 1–60 min.

Comparison of the effects of L-NMA in the presence of propofol and intralipid indicated that in the presence of propofol, L-NMA produced a more pronounced decrease in HR at 15 and 45 min and a less pronounced carotid vasoconstriction.

Discussion

Plasma concentrations of propofol were not measured in our study. However, Goodchild and colleagues[17] have previously shown that infusions of 0.33 and 0.66 mg kg^{-1} min^{-1} led to plasma concentrations of 2–13 μg ml^{-1} in dogs, which is within the anaesthetic range in humans. Thus, the propofol infusion rate used in our study most likely correlated with clinically relevant propofol concentrations.

Moreno and colleagues[18] reported that *in vitro* propofol did not affect mesenteric vascular tone at concentrations <10^{-3}M. Brooke and colleagues[19] reported that propofol does not affect renal BF *in vivo*. Although in our model propofol induced increases in carotid and coronary BF, it did not affect hepatic, portal, mesenteric, renal or vertebral BF. Therefore, our *in vivo* data confirm that propofol did not affect the mesenteric and renal circulations, and that the effects of propofol remain selective to regional circulation. Since intralipid did not affect either carotid or coronary BF, our data also suggest that the increases in coronary and carotid BF were specific to propofol and were not related to the presence of intralipid.

Our data also confirm that propofol induces a systemic vasodilatation associated with tachycardia and a decrease in

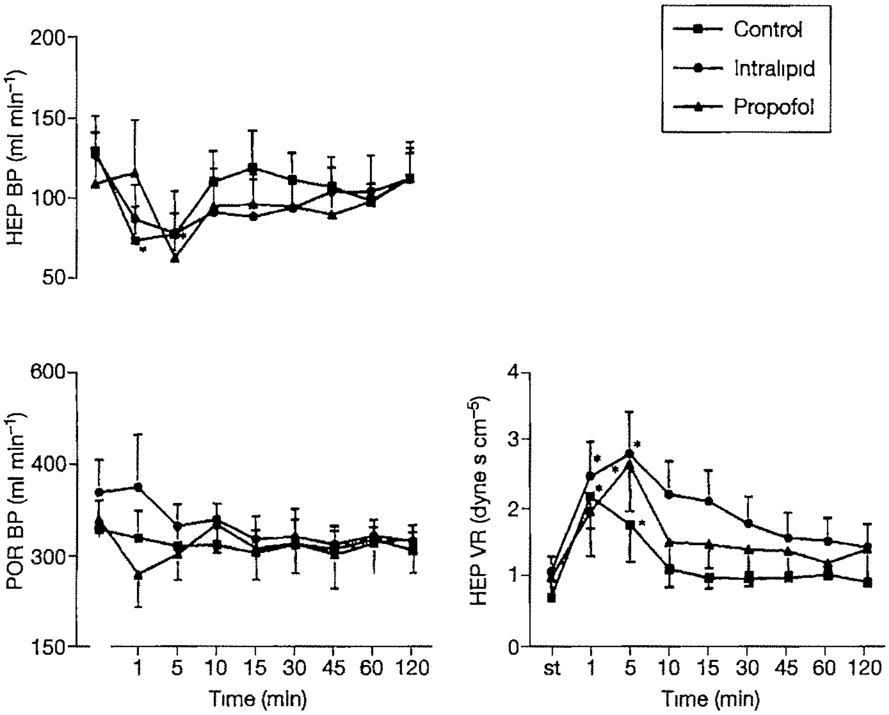


Fig 4 Effects of nitric oxide synthase inhibition using *N*-methyl-L-arginine (L-NMA) in awake dogs (n=11) and during propofol infusion (n=8) and during intralipid (n=6) infusion on hepatic (Hep) and portal (Por) blood flow (BF) and vascular resistance (VR) Data are mean (SEM). $^*P$<0 05 *vs* steady state.

myocardial contractility. These effects on cardiac function were associated with an increase in carotid and coronary BF. Using a similar experimental design, Wouters and colleagues,[20] Pagel and colleagues,[1] and Moore and colleagues[21] also reported an increase in coronary BF after propofol injected as a bolus. Yamanoue and colleagues[22] and Gacar and colleagues[5] demonstrated that, *in vitro*, propofol relaxes the coronary artery only at high concentrations. The short-lasting coronary vasodilatation was most likely indirect and related to the associated tachycardia via an increase in myocardial oxygen demand.

In assessing the role of the NO pathway in propofol-mediated haemodynamic changes, we hypothesized that: (i) the lack of difference in the effect induced by L-NMA in the presence of either propofol or intralipid compared with control indicated no interaction between the NO pathway and either intralipid or propofol; (ii) similar changes induced by L-NMA in the presence of both intralipid and propofol reflected an intralipid interaction; (iii) changes induced by L-NMA in the presence of either intralipid or propofol represented a propofol effect if recorded only in the presence of propofol, or represented opposite effects of intralipid and propofol if recorded only in the presence of intralipid.

Terragno and colleagues[23] developed the concept that factors regulating regional BF vary according to experimental conditions. Our data indicate that in the presence of intralipid, the NO pathway plays a more important role in the local modulation of carotid, renal and mesenteric tone. Thus, in the presence of intralipid, the blockade of NOS resulted in more pronounced carotid, renal and mesenteric vasoconstriction as compared with control experimental conditions. Since propofol did not produce similar effects, it seems that the effects of propofol alone on the mesenteric and renal circulation are opposite to the effects produced by intralipid (i.e. propofol inhibited rather that stimulated the NO pathway). Indeed, in the presence of propofol the intralipid-mediated increased activity of NOS was abolished

Furthermore, our data also confirm that the role of the NO pathway in the modulation of local circulation varies according to the territory. NO plays a minor role in the coronary circulation, whereas the role played by NOS in the carotid and renal circulations is more significant. However, our data support the concept that propofol inhibits rather than stimulates the NO pathway in these vascular beds. Thus, L-NMA produced similar carotid and renal vasoconstriction in control experimental conditions and in the presence of propofol whereas the renal and carotid vasoconstriction was accentuated in the presence of intralipid.

The effects of propofol and its solvent intralipid on the effects of L-NMA-associated changes in cardiac function are more complex. It is well established that under physiological conditions, the recorded increase in afterload produces a reflex-mediated decrease in HR and CO. L-NMA failed to increase HR initially in the presence of both propofol and intralipid. However, we recorded a secondary decrease in HR in the presence of both propofol and intralipid. Although CO remained unchanged in the presence of intralipid, changes in CO were similar in control experimental conditions and during propofol infusions. In these experimental conditions, CO did not decrease, suggesting that the presence of intralipid prevented the systemic vasoconstriction-mediated decrease in HR. The presence of intralipid also prevented the L-NMA-mediated decrease in CO, indicating an intralipid-related increase in venous return.

In summary, our data demonstrate that propofol produces selective regional haemodynamic changes. The stimulation of the NO pathway did not contribute to the regional changes mediated by propofol itself. This study also demonstrated that intralipid and not propofol stimulates the NO pathway.

Acknowledgements

The authors would like to thank Brice Chelly for technical assistance and Anne Starr for the preparation of the manuscript

References

1 Pagel PS, Warltier DC. Negative inotropic effects of propofol as evaluated by the regional preload recruitable stroke work relationship in chronically instrumented dogs *Anesthesiology* 1993; **78**: 100–8

2 Lowe D, Hettrick DA, Pagel PS, Warltier DC. Propofol alters left ventricular afterload as evaluated by aortic input impedance in dogs. *Anesthesiology* 1996; **84**: 368–76

3 Robinson BJ, Ebert TJ, O'Brien TJ, Colinco MD. Mechanisms whereby propofol mediates peripheral vasodilation in humans. *Anesthesiology* 1997; **86**: 64–72

4 Chang KS, Davis RF. Propofol produces endothelium-independent vasodilation and may act as a Ca^{2+} channel blocker. *Anesth Analg* 1993; **76**. 24–32

5 Gacar N, Gok S, Kalyoncu NI, Ozen I, Soykan N, Aktürk G The effect of endothelium on the response to propofol on bovine coronary artery rings. *Acta Anaesthesiol Scand* 1995; **39**: 1080–3

6 Petros AJ, Bogle RG, Pearson JD. Propofol stimulates nitric oxide release from cultured porcine aortic endothelial cells. *Br J Pharmacolol* 1993, **109**: 6–7

7 Horibe M, Ogawa K, Sohn JT, Murray PA Propofol attenuates acetylcholine-induced pulmonary vasorelaxation. role of nitric oxide and endothelium-derived hyperpolarizing factors. *Anesthesiology* 2000; **93**: 447–55

8 Hageman JR, McCIulloch K, Gora P, Olsen EK, Pachman L, Hunt CE. Intralipid alterations in pulmonary prostaglandin metabolism and gas exchanges. *Crit Care Med* 1983, **11**: 794–8

9 Nakamura K, Hatano H, Hirakata H, Nishiwada M, Toda H, Mori K. Direct vasoconstrictor and vasodilatator effects of propofol in isolated dog arteries. *Br J Anaesth* 1992; **68**: 193–7

10 Ohashi Y, Katayama M, Hirata K, Suematsu M, Kawashima S, Yokoyama M. Activation of nitric oxide synthase from cultured aortic endothelial cells by phospholipids. *Biochem Biophys Res Commun* 1993; **195**: 1314–20

11 Kugiyama K, Kerns SA, Morrisett JD, Roberts R, Henry PD. Impairment of endothelium-dependent arterial relaxation by lysolecithin in modified low-density lipoproteins. *Nature* 1990; **344**: 160–2

12 Yokoyama M, Hirata K, Miyake R, Akita H, Ishikama Y, Fukuzaki H. Lysophosphatidylcholine: essential role in the inhibition of endothelium-dependent vasorelaxation by oxidized low density lipoprotein. *Biochem Biophys Res Commun* 1990; **168**: 301–8

13 Merin RG, Bernard JM, Doursout MF, Cohen M, Chelly JE Comparison of the effects of isoflurane and desflurane on cardiovascular dynamics and regional blood flow in the chronically instrumented dog. *Anesthesiology* 1991; **74**: 568–74

14 Hartley CJ, Cole JS. An ultrasonic pulsed Doppler system for measuring blood flow in small vessels. *J Appl Physiol* 1994; **37**: 626–9

15 Ishida T, Lewis RM, Hartley CJ, Entman ML, Field JB: Comparison of hepatic extraction of insulin and glucagons in conscious and anesthetized dogs. *Endocrinology* 1983; **112**: 1098–9

16 Kilbourn RG, Owen-Schaub LB, Cromeens DM, et *al* NG-methyl-L-arginine, an inhibitor of nitric oxide formation, reverses L-2-mediated hypotension in dogs. *J Appl Physiol* 1994; **76**: 1130–7

17 Goodchild CS, Serrao JM. Cardiovascular effects of propofol in the anaesthetized dog. *Br J Anaesth* 1989; **63**: 87–92

18 Moreno L, Martinez-Cuesta MA, Muedra V, Beltran B, Esplugues J. Role of the endothelium in the relaxation induced by propofol and thiopental in isolated arteries from man. *J Pharm Pharmacol* 1997; **49**: 430–2

19 Brooke M, Armstrong C, Hinder F, Conroy B, Traber LD, Traber DL. The effects of propofol on haemodynamics and renal blood flow in healthy and in septic sheep. *Anesth Analg* 1996; **82**: 738–43

20 Wouters PF, Van de Velde MA, Marcus MAE, Deruyter HA, Van Aken H. Hemodynamic changes during induction of anaesthesia with Eltanolone and Propofol in dogs. *Anesth Analg* 1995; **81**: 125–31

21 Moore PG, Kien ND, Boldy RM, Reitan JA. Comparative effects of nitric oxide inhibition on the coronary vasomotor responses to etomidate, propofol and thiopental in anesthetized dogs. *Anesth Analg* 1994; **79**: 439–46

22 Yamanoue T, Brum JM, Estafanous FG. Vasodilation and mechanism of action of propofol in porcine coronary artery. *Anesthesiology* 1994; **81**: 443–51

23 Terragno NA, Terragno DA, McGiff JC. Contribution of prostaglandins to the renal circulation in conscious, anesthetized and laparotomized dogs. *Circ Res* 1977; **40**: 590–5

British Journal of Anaesthesia 89 (3): 499–508 (2002)

BJA

REVIEW ARTICLE

Maternal deaths from anaesthesia. An extract from *Why Mothers Die 1997–1999*, the Confidential Enquiries into Maternal Deaths in the United Kingdom†

T. A. Thomas[1] and G. M. Cooper[2]*, on behalf of the Editorial Board of the Confidential Enquiries into Maternal Deaths in the United Kingdom‡

[1]Department of Anaesthesia, St Michael's Hospital, Southwell Street, Bristol BS2 8EG, UK. [2]University of Birmingham, Department of Anaesthesia and Intensive Care, Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TH, UK

**Corresponding author*

This article is reprinted from *Why Mothers Die 1997–1999*, the fifth report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. RCOG Press, 2001; 134–49. Reproduced with permission from the Editorial Board.

Br J Anaesth 2002; **89**: 499–508

Keywords: anaesthesia, obstetric; anaesthetic techniques, epidural; anaesthesia, general; complications

The central assessors in anaesthesia reviewed the cases of all the women in this report identified as having received an anaesthetic for this triennium, some 142 cases. In looking at the individual cases the assessors were struck by the high standards of anaesthetic care generally provided, sometimes in difficult circumstances. In most cases the standard of record keeping was also high. However, there are areas of concern about the consistency of anaesthetic services between units. Reviewing the records showed that in some places the quality and quantity of anaesthesia service does not meet the declared standards of the relevant professional bodies.

In deciding the likely cause of death, the evidence had to be weighed up without the benefit of questioning all those involved in a patient's care. Much reliance is placed on the local assessors and their ability to make discreet enquiries. Sometimes, even after coroner's inquests, the cause of death was unclear. It was therefore a matter of judgement assigning a death as being a direct result of anaesthesia, or whether substandard care contributed to the demise. Key points of the cases illustrated here result from the central assessors' judgement, bearing in mind that the purpose of the exercise is to learn from errors and improve patient care in the future.

The challenges presented to the obstetric anaesthetist are increasing in number, complexity and severity. Many sick mothers have received anaesthetics safely and anaesthetists are accepting an increasing responsibility for aspects of mother's care that fall naturally within their competence and control. Anaesthetists are trained to recognize and treat major haemorrhage that they encounter in many areas of their professional practice. Obstetric haemorrhage is sometimes more difficult to manage appropriately. Nevertheless it is disappointing to record substandard aspects of anaesthetic care in seven deaths due to haemorrhage.

Conduct of anaesthesia includes preoperative preparation, delivery of anaesthesia, and postoperative recovery. In this triennium, there was one anaesthetic death ascribed as being directly due to the conduct of anaesthesia for Caesarean section, in particular to the administration of oxytocin in a compromised patient. Two other deaths are ascribed to anaesthetics given after prolonged and complex

---

†This article is accompanied by Editorial I.

‡Editorial Board: Gwyneth Lewis MSc, MRCGP, FFPHM, FRCOG, Director and Editor, James Drife MD, FRCOG, FRCPEd, FRCSEd, Clinical Director, Beverley Botting BSc Hon MFPHM, Christine Carson SRN SRM, PGDip MSc, Griselda Cooper FRCA, Marion Hall MD FRCOG, Catherine McCormick RN RM, James Neilson MD FRCOG, Margaret Oates FRCPsych, Robert Shaw MD FRCSEd, FRCOG, Michael de Swiet MD FRCP, Harry Millward-Sadler FRCPath, MHSM, Trevor Thomas FRCA, William Thompson MD FRCOG, Sheila Willatts MD FRCA FRCP

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

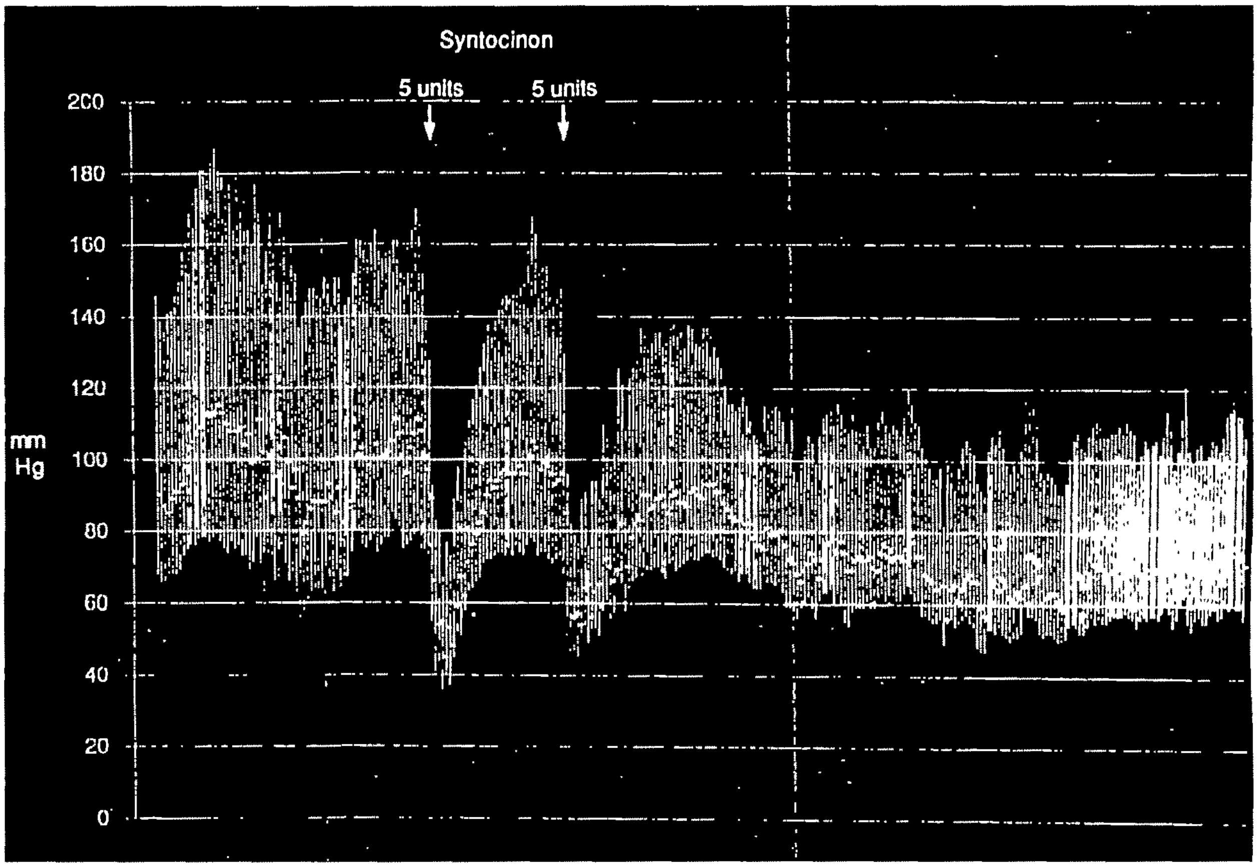


Fig 1 Arterial pressure in a patient during Caesarean section under spinal anaesthesia; note the decrease in arterial pressure after 5 iu of Syntocinon on two occasions (Courtesy of Dr T. H Clutton-Brock and G M Cooper)

care in intensive care units (ICU). In both of these cases the patient's condition was improving but further surgical treatment was needed. Death resulted from complications of anaesthesia for that surgery.

Deaths due to anaesthesia

There were three deaths in this triennium that were directly due to actions or omissions of anaesthesia services or staff.

Case 1

A woman requested epidural analgesia during her labour. An epidural catheter was sited but a test dose of 0.25% bupivacaine 4 ml resulted in a high sensory and motor block within 2–3 min. Clear fluid aspirated from the catheter tested positive for sugar. A diagnosis of subarachnoid catheter placement was made.

It was decided to use the subarachnoid catheter for labour analgesia. All subsequent injections of bupivacaine were given by an anaesthetist and the quality of resulting analgesia was described as good. Seven hours later labour had failed to progress, in spite of oxytocin augmentation, and it was decided to deliver the fetus by Caesarean section. Anaesthesia was not adequate for Caesarean section so a top-up injection of 0.5% plain bupivacaine 2 ml was given from a 20-ml syringe. The spinal block spread higher than expected. The woman experienced difficulty breathing and then lost consciousness. She developed a bradycardia of 30 beats min^{-1} and the systolic arterial pressure decreased to 60 mm Hg. The patient was intubated promptly and given fluids, ephedrine, atropine and epinephrine. Cardiac output was restored but the arterial pressure had increased only to 80 mm Hg systolic when the baby was born, apnoeic and pulseless. The paediatrician had not arrived and the anaesthetist was asked to intubate and resuscitate the baby. By the time the anaesthetist had completed the resuscitation, the obstetrician had discovered an adherent placenta and the mother was losing blood. The obstetrician requested oxytocin (Syntocinon) to improve uterine tone. The anaesthetist was reluctant because the systolic arterial pressure was only 60 mm Hg. After rapid infusion of i.v. colloid solution and further epinephrine, oxytocin 10 iu was given. Cardiac arrest occurred almost at once. Resuscitation followed accepted practice but was unsuccessful.

High spinal block, bradycardia and hypotension are recognized complications of spinal anaesthesia. The cardiovascular complications involve complex reflexes,[8] that are still not widely understood. They are sometimes difficult to treat especially when drugs with cardiovascular side-effects further complicate the clinical picture.

Whether the use of hyperbaric bupivacaine would have limited the cephalic spread and avoided the high block is questionable. The literature would suggest not. However, using a 20-ml syringe to measure 2 ml does not ensure great accuracy. Syringes of 2-, 3- or 5-ml capacity are available and employed because additional fractions of a millilitre of bupivacaine can affect the extent of a subarachnoid anaesthetic.

In this case, the patient was initially resuscitated effectively but the hypotension was not completely reversed when the anaesthetist was asked to resuscitate the baby. At the time, the maternal arterial pressure was 80 mm Hg systolic. The baby was resuscitated quickly and effectively. However, the anaesthetist's full attention was distracted from the mother. In that time, the maternal systolic arterial pressure had decreased to 60 mm Hg. Uterine hypotonia occurred and the obstetrician asked for oxytocin 10 iu to be given. This is a common obstetric request during Caesarean section.

It is not widely appreciated that the dose recommended in the *British National Formulary*[4] (and other formularies[7 12]) is 5, not 10, units. The *British National Formulary* states: 'Dose: Caesarean section, *by slow intravenous injection* immediately after delivery, 5 units'. Oxytocin has a direct relaxant effect on vascular smooth muscle. Under normal circumstances, there is a reflex tachycardia and increased cardiac output that accompanies the transient decrease in arterial pressure as shown in Figure 1. However, the hypovolaemic patient (or one with compromised cardiac function) may not respond in the normal way. In such circumstances the drug may have lethal effects, and among the contraindications to its use is severe cardiovascular disease.[4]

The administration of oxytocin in the presence of a high spinal block, hypotension and recent bradycardia, accompanied by bleeding at Caesarean section produced a situation from which the patient could not be rescued. Oxytocin has peripheral and central cardiovascular receptor sites and complex cardiovascular actions.[5 11]

Every medical practitioner administering any drug is responsible for ensuring that the drug, its dose and method or route of administration are correct and appropriate. A request from another practitioner does not absolve him or her from this responsibility.

The assessors appreciate the difficulties in this case. Anaesthetists should remember that their primary responsibility is to the mother,[1] and that they must summon help at the first signs of unexpected reactions to treatment.

Case 2

The second patient received five anaesthetics, the first for a Caesarean section during which she suffered a major obstetric haemorrhage. She then required several further operations to control the bleeding. During the fourth, abdominal packs were placed to control continuing venous bleeding and the patient returned to the ICU intubated and ventilated. She was successfully weaned from the ventilator and extubated 24 h later. Two days later, removal of the abdominal packs was planned. The patient was taken to theatre from ICU with invasive cardiovascular monitoring in place. There is no record of any gastric secretion prophylaxis prior to this anaesthetic.

After preoxygenation, anaesthesia was induced using propofol 120 mg and fentanyl 100 µg. Muscle relaxation was achieved with cisatracurium 14 mg. There was no mention of cricoid pressure. These two facts suggest that a rapid sequence induction technique was not used on this occasion. Pulmonary aspiration of fluid occurred. The aspirate was tested and gave an acid reaction. Surgery was completed successfully. The patient was extubated and returned to ICU. Her condition slowly deteriorated and she was re-intubated and required artificial ventilation 24 h later. Aspiration pneumonitis was subsequently diagnosed on x-ray appearances. She continued to deteriorate and died some 12 days later.

This patient was rescued from life-threatening problems, receiving anaesthesia without mishap on the first four occasions. There were many factors that could have contributed to the eventual organ failure, but it is difficult to ignore the fact that her condition had been improving, until the pulmonary aspiration. Given the patient's previous problems and the fact that she came to theatre from ICU for removal of abdominal packs, acid prophylaxis and a rapid sequence induction were indicated. There is no record that these precautions were taken. These omissions constitute substandard anaesthetic care.

Case 3

A multiparous woman received a general anaesthetic for a Caesarean delivery. She had suffered postpartum haemorrhages after earlier deliveries. Her blood was known to be difficult to crossmatch because of antibodies, and she had failed to keep a blood transfusion service antenatal appointment to plan future haematological care. She was therefore a high-risk case. In spite of these known problems, blood was not crossmatched when labour began.

As blood was not available when bleeding occurred at Caesarean section, large volumes of colloid and crystalloid were needed to maintain cardiovascular stability. Carboprost was used to control bleeding after which bronchospasm and crepitations were detected. Over-transfusion was diagnosed. Direct transfer from theatre to ICU was arranged. Treatment in ICU was successful in stabilizing the patient for the first 2–3 days. However, after 4–5 days, she became anuric and she was transferred to another ICU for haemodialysis and further respiratory support including tracheostomy. Respiratory performance improved. The first tracheostomy tube either blocked or became displaced. Attempts to change it were not successful and a tracheal tube was introduced via the tracheostomy site.

The ICU did not have a small enough fibreoptic bronchoscope to perform an examination via the tracheal tube that had been passed so elective revision of the tracheostomy was attempted. During this procedure, difficulties with the airway and ventilation were experienced. Jet ventilation was used in an attempt to overcome the problem. Surgical emphysema was detected. Eventually the airway was lost and death resulted.

At some stage, the tracheal tube became extratracheal and jet ventilation probably caused the surgical emphysema. At post-mortem, a number of tears were identified in the trachea and bronchi and surgical emphysema of the mediastinum and subcutaneous tissues was confirmed.

Although death resulted from the difficult airway problem, substandard care was present in several aspects. First, the failure to crossmatch blood for this high-risk mother when she was admitted in labour led to intraoperative difficulties which, in turn, contributed to the need for ICU admission. Second, there seems to have been little understanding that the side-effects of carboprost include bronchospasm and pulmonary oedema. Third, there was a failure to site a central venous pressure (CVP) line in theatre when it might have helped to differentiate between the possible causes of pulmonary oedema and to guide fluid therapy. Whether it would have changed the outcome is conjectural. Fourth, in the second ICU there was no access to the fibreoptic endoscope of the size needed for endoscopy via a 6.0-mm tracheal tube. This examination might have given a better understanding of the airway dimensions and condition before the tracheostomy revision was attempted. This knowledge may have allowed better preoperative preparation and may have prevented the death.

Deaths to which anaesthesia contributed

In addition to the three deaths detailed above, there were a number of deaths that contain messages for anaesthesia services. In some, anaesthesia care was regarded as substandard. These deaths have been subdivided as follows although, inevitably, there is overlap between the categories.

(i) Lack of multidisciplinary co-operation (seven deaths, one also counted in haemorrhage).

(ii) Major obstetric haemorrhage (six deaths, one also counted in poor co-operation).

(iii) Poor postoperative care (three deaths).

(iv) Lack of appreciation of severity of illness (two cases are described here as illustrations, but failure to recognize the severity of illness was present to some degree in most of the cases counted in categories 1,2, 3 and 5).

(v) Sepsis (two deaths).

(i) Lack of multidisciplinary co-operation

Obstetricians failed to give adequate warning of impending problems to anaesthetic departments in at least six of the maternal deaths in this triennium. The lack of consultation with anaesthetic colleagues contributed significantly to a number of these deaths. The lessons from the following examples need to be widely disseminated. All team members need to be aware of the vital contributions that can be made by anaesthesia when adequate warning is given and the harm that can result when it is not. Obstetric anaesthetists must also remember that they have colleagues with different, but invaluable skills, provided the anaesthetist calls on their help in good time

Case 4

A morbidly obese woman became increasingly short of breath towards the end of her pregnancy. An initial diagnosis of pulmonary embolism was made but subsequently excluded. She developed a tachycardia of 120 beats min^{-1}, oedema and proteinuria over a period of several days during which she was an in-patient. An elective Caesarean section was planned but there was no anaesthetic consultation until the day before the planned operation. At that time, the anaesthetist obviously thought that cardiac problems might exist because echocardiography was considered but it was rejected because obesity was thought to make the investigation unreliable. On the day of operation invasive monitoring was thought necessary but it was abandoned after initial failures to site the lines. General anaesthesia was chosen because the obesity and shortness of breath made lying down difficult. However, an epidural catheter was placed successfully and tested. General anaesthesia was induced using a rapid sequence technique. The patient arrested almost immediately after injection of thiopental and could not be resuscitated. At post-mortem, a cardiomyopathy was diagnosed.

Care was substandard because there was no consultation with the anaesthesia service during the 6 days she was in hospital. Anaesthetic care was also substandard because further investigations should have been done preoperatively to properly evaluate her breathlessness. While it is true that obesity makes echocardiography more difficult and less informative, it might have been a helpful investigation and was worth attempting. Furthermore, perseverance with siting direct monitoring for this elective case could have involved attempts by other staff with more expertise. Direct arterial pressure monitoring might have improved the detection of problems and assessment of resuscitation efforts.

Having sited an epidural in such a difficult case, it is hard to understand why a regional technique was not at least attempted. Whether the use of the epidural would have changed the outcome is not possible to say, but at least the potentially safer technique would have been attempted.

The next four cases are described as examples of lack of consultation with, and involvement of, anaesthesia services. Criticism is of the failure to communicate not of the anaesthetists involved.

Case 5

A woman with a multiple pregnancy developed proteinuria and subsequently hypertension. She was admitted as an emergency 4 weeks later, at 35 weeks of gestation with severe epigastric pain and pre-eclampsia requiring treatment with magnesium sulphate. She became unconscious because of a cerebral bleed but delivery and help from the anaesthetist were delayed for a further 8 h.

It is obvious that a multidisciplinary approach should have been adopted as soon as she came into hospital.

Case 6

A multiparous woman had previous children who had died of pulmonary hypertension and she herself had the same diagnosis made during this pregnancy. A termination of pregnancy was offered but she declined. She was admitted to hospital late in the second trimester with severe right heart failure and transferred to the coronary care unit, but when she started having spontaneous contractions she was sent to the labour ward. She had a spontaneous delivery but she arrested immediately after being given oxytocin (Syntocinon) 10 iu. Cardiopulmonary resuscitation was successful in restoring spontaneous rhythm and breathing resumed, but she died a day later in the coronary care unit.

Substandard care was evident despite likely inevitable death. No consultations had taken place with the anaesthetic team. Monitoring of her cardiovascular status during labour should have included at least direct arterial pressure and CVP. Pulmonary artery pressure measurements could also have informed the team caring for her. Anaesthetic services could have set up this monitoring. As in Case 1, the dose and method of administration of oxytocin were inappropriate.

Case 7

A woman had an uneventful multiple pregnancy until she was admitted to hospital near term with vomiting and rigors. On admission she was obviously very sick with a pyrexia of 40.5°C, hypotension (systolic pressure of 70 mm Hg), tachycardia (132 beats min^{-1}), dehydration and ketosis. The babies died. Spurious high recordings were obtained on a non-invasive arterial pressure machine although her real arterial pressure was barely recordable. It was not until more than 3 h later that an anaesthetist was called because a midwife had difficulty taking blood. As the consultant anaesthetist arrived, the patient collapsed, was cyanosed and her arterial pressure was unrecordable. Disseminated intravascular coagulation (DIC) was developing. A central venous line was inserted and further help obtained from intensivists. Despite Caesarean section, supportive treatment, and intensive care, the patient died of multiple organ failure 3 days later.

It was only because the midwife could not obtain a blood sample that an anaesthetist was called. By then the patient was *in extremis*. This lack of appreciation of the need and value of multidisciplinary care is lamentable (indeed also the implication that the anaesthetic team are mere technicians). Thereafter it was all too late. The practice of depending only on automatic arterial pressure measurement rather than assessing the patient as a whole is to be deprecated.

Case 8

A woman who spoke little English had her labour induced and had a traumatic ventouse delivery with bleeding. Laparotomy was performed to tie off her internal iliac vessels, but hysterectomy proved necessary. A massive blood transfusion was required. She had a prolonged period of care in ICU but eventually recovered. Some time later it was realized she had a vesicovaginal fistula that was repaired as an elective procedure some months after delivery. Her preoperative condition seems to have been satisfactory but there was no record of electrolyte or liver function tests being performed. Anaesthesia proceeded uneventfully with stable heart rate and arterial pressure. The operation took just under 90 min. The anaesthetist prescribed a postoperative fluid regimen of dextrose/saline 1000 ml 8 hourly. Subsequently, the gynaecologist requested a postoperative urine output of at least 15 ml quarter hourly. In order to achieve this, the senior house officer in gynaecology increased the prescribed i.v. fluids such that 5 litres dextrose saline were received overnight. The following morning, the patient suffered a seizure and cerebellar coning. She was found to be hyponatraemic (Na^+ 122 mmol litre^{-1}). She was intubated and ventilated but died a few days later without regaining consciousness.

This *late* death is all the more poignant because the patient had survived a catastrophic postpartum haemorrhage. After the subsequent fistula repair the management of i.v. fluid therapy was clearly ill understood. Discussion with the anaesthetist might have prevented the unwise prescription change. What may not be widely appreciated is the increased susceptibility of premenopausal women to the effects of acute hyponatraemia.[3] Respiratory arrest and seizures occur at a higher plasma sodium in women (95% confidence limits, 95–130 mmol litre^{-1}) than in men (95% confidence limits, 92–115 mmol litre^{-1}) and at a significantly higher plasma sodium in menstruant women than in postmenopausal women.[2]

Case 9

A woman had a medical history that included bicornuate uterus, uterine surgery to correct it, previous Caesarean section, and a recognized placenta praevia in the current pregnancy. She spent the last weeks of her pregnancy as an in-patient. She had a preoperative haemoglobin of 9.1g dl^{-1} and was clearly a very high-risk patient. The obstetric service had more than a month to make the necessary consultations and arrangements to ensure consultant anaesthetist involvement for the planned elective Caesarean section. However, contact with the anaesthesia service was delayed until the day before the planned operation because the surgeon did not anticipate problems. Two inexperienced trainees provided anaesthesia because there was no consultant available on the day of operation. A general anaesthetic was given using a standard technique. The case was apparently started with only one peripheral i.v. cannula sited. The case was uneventful until a major haemorrhage occurred. The woman suffered a blood loss, according to the anaesthetists, of 6.5 litres. In spite of the major blood loss and limited venous access, initial resuscitation was ultimately successful. However, the patient suffered 45 min of hypotension and the lack of CVP monitoring must have made it difficult to judge the adequacy of fluid replacement. The patient was transferred from theatre to the high dependency unit where she suffered further blood loss necessitating laparotomy. She died shortly after induction of anaesthesia for this surgery.

This case is included here because it illustrates so clearly how inadequate communication with anaesthesia services can lead to trainees treating cases and circumstances far beyond their experience and abilities. In this case, absence of a second i.v. cannula hampered fluid replacement and exposed the woman to a long period of hypotension. In addition, lack of a CVP line impaired recognition of blood loss. There was clearly an opportunity to site both before the woman left theatre. However, inexperience probably led to a false sense of security and the opportunity was not taken. Failing to do so hampered diagnosis and treatment of the continuing bleeding postoperatively.

The second anaesthetic was given in difficult circumstances. The woman had bled a large volume and the cardiovascular decompensation that followed induction was probably due to inadequate blood volume replacement. It might have been prevented if earlier haemorrhage and subsequent resuscitation had been better monitored. Poor anaesthesia care therefore contributed to this death.

Having made these comments, the main failure in the case was in communication and cooperation between specialties. Inadequate warning was given to the anaesthetic service. The Caesarean section was an elective procedure with very high-risk factors. Once the difficulty of providing a consultant anaesthetist was recognized it could have been delayed until senior anaesthetist input and full monitoring were available.

(ii) Major obstetric haemorrhage

Major haemorrhage is still one of the commonest causes of maternal death. It may complicate either Caesarean delivery or other obstetric surgery such as termination of pregnancy or removal of retained products of conception. Anaesthetists are trained to recognize the effects of major haemorrhage and to treat it appropriately. In a number of cases in this triennium they failed to exercise that skill. A small number of these women died in theatre, either during their initial operation or during surgical attempts to stop haemorrhage. Many of the women, however, were resuscitated in theatre and transferred to the ICU for further treatment. These transfers were often made directly from theatre, although in a small number of cases women were returned to postnatal or recovery rooms or wards because the severity of their clinical condition had not been recognized.

Assessments of cardiovascular stability were often based only on non-invasive arterial pressure and pulse rate measurements. Estimation of blood loss at Caesarean section or during evacuation of *retained* products of conception is known to be extremely difficult and is often inaccurate. The severity of haemorrhage can be better judged by looking for the physiological responses to it rather than by trying to guess the amount of blood loss visually. CVP measurement, when made in conjunction with systemic arterial pressure, pulse rate, urine output and visual assessment of the patient's pallor will give a better, more accurate assessment of the true cardiovascular state. Anaesthetists are skilled in the insertion and interpretation of CVP monitoring. When the internal jugular or subclavian routes are felt to be inappropriate, access may be gained from the antecubital veins. Failing to use this monitoring in the treatment of major obstetric haemorrhage is substandard care. In many cases, anaesthetists were called on to manage i.v. fluid replacement or resuscitate the mother. Responsibility for substandard care in such circumstances must rest with the anaesthetic services.

In looking at some of the deaths attributed to haemorrhage, multifactorial causation is clear. Pathological process, poor obstetric management/care, poor inter-specialty communication and inadequate anaesthetic response all appear in various combinations. The following two cases serve to illustrate most of these deficiencies.

Case 10

A woman suffered an early fetal loss and was anaesthetized for evacuation of retained products by a junior trainee anaesthetist. After the surgery, she continued to lose blood *per vaginam*. On return to theatre she was again anaesthetized by a junior anaesthetist. Consultant input into her care did not begin for another hour. She eventually underwent hysterectomy. During the operation, she suffered further major haemorrhage but blood replacement was limited to 5 units of blood. Maintenance of her arterial pressure required methoxamine and norepinephrine throughout the operation. Transfer to ICU was intended but while being moved to her bed she arrested. Although she was resuscitated from this arrest she died shortly after in ICU.

Anaesthetic services must carry some responsibility for this death. Management of a patient suffering continuing vaginal bleeding after evacuation of retained products of conception should not be left to a junior trainee. It took 1 h for senior anaesthetic assistance to be summoned. This is substandard care.

Management of the patient subsequently seems to have followed widely accepted practice but inspection of the record would indicate that she received only 5 units of blood during a 2-h procedure during which she experienced major haemorrhage. Methoxamine and norepinephrine were used freely during the same period. It would seem that the anaesthetists achieved acceptable arterial pressure recordings by producing profound vasoconstriction. This may be an appropriate temporary measure in the face of major haemorrhage but is not, ultimately, the solution of the problem. There is a note indicating that the patient was peripherally shut down before the second anaesthetic began. The inference from the information available is that inadequate quantities of blood were given. There is no record of haematological investigations of haemoglobin or packed cell volume that might cast further light on these circumstances. However, the fact that the patient suffered a cardiac arrest during transfer from the operating table to her bed seems to indicate that the appropriate cardiovascular stability had not been achieved whilst in theatre.

Case 11

A woman who did not speak English had an urgent Caesarean section and returned to theatre 2 h later because of bleeding. She was tachycardic (140 beats min^{-1}) and the coagulation screen was abnormal. After the second general anaesthetic she was extubated, but her oxygen saturation varied between 85 and 93%. Two hours later pulmonary oedema was diagnosed and she was reintubated. She had two more laparotomies for bleeding and died several days later.

Amniotic fluid embolism seemed the most likely diagnosis but it was not confirmed histologically. Although it would probably have made no difference to the eventual outcome, it represents substandard care not to have sought help and instituted CVP and arterial monitoring when this woman first returned to theatre with evidence of a coagulopathy.

(iii) Poor postoperative care

There were three deaths in this triennium in which poor postoperative care was a contributing factor, two of which are described here.

Case 12

A woman had a Caesarean section in which anaesthesia was provided with a combined spinal–epidural technique. Within a few hours she developed a severe headache and hypertension. The anaesthetist treated this as a postdural puncture headache and gave a blood patch through the epidural catheter. She later developed slurred speech, constant vomiting and a hemiparesis followed by convulsions for which she received magnesium sulphate. She was transferred for computerized tomography that showed a subarachnoid haemorrhage. Despite intensive care, she died some days later.

This case is one of several deaths from subarachnoid haemorrhage. Whilst the ultimate outcome is unlikely to have been different, the diagnosis of postdural puncture headache so soon after a spinal with an atraumatic needle is unlikely.

Case 13

The anaesthetist was not informed about a woman with severe hypertension (250/140 mm Hg) and proteinuria until Caesarean section was required at night. The patient was receiving hydralazine, labetalol and nifedipine. Her arterial pressure decreased to normal values after induction of general anaesthesia. Magnesium sulphate was given during the procedure. The operation lasted 1 h 45 min. Blood loss was estimated at 1500 ml to 2 litres, yet no blood was given. Fluid replacement comprised only 2000 ml crystalloid, and 500 ml colloids were given during surgery At the end of surgery her tachycardia persisted. Shortly after leaving the patient in recovery, the anaesthetist was called back because the arterial pressure was 48/23 mm Hg. Transfusion with O negative blood was started. The nursing staff asked the anaesthetist to stay in recovery because they were concerned about the patient's condition. Nevertheless the anaesthetist seems to have left recovery. Two hours after reaching recovery the woman suffered a cardiac arrest and attempts at resuscitation were futile.

There were a number of aspects of substandard care, including the lack of senior involvement and poor fluid management. The anaesthetist's responsibility to the patient does not end with transfer to the recovery room. There remains a duty to ensure the patient's full recovery from their anaesthetic and operation. The duty can be discharged directly or by transfer to a site where that recovery can be monitored and completed. Abandoning the patient in recovery, having been alerted to her parlous state, represents gross substandard care.

(iv) Lack of appreciation of severity of illness

The following cases illustrate a common theme showing how failure to realize the severity of illness meant that senior help was sought too late.

Case 14

A woman with learning difficulties had a septic fetal loss and required an anaesthetic for removal of a retained placenta. There was a 2-day history of diarrhoea and the patient was tachycardic (125 beats min^{-1}) and hypotensive (systolic arterial pressure 60 mm Hg). The clinical assistant discussed the case with a trainee in anaesthesia but both failed to realize the severity of illness or call for help. After 3 litres of fluid, the patient was still tachycardic and the systolic arterial pressure was 100 mm Hg. Antibiotics were given at manual removal, but not earlier. The patient went to recover in a side room because of the pregnancy loss. Half an hour later, she lost consciousness, had difficulty breathing, and her oxygen saturation was low. At that point a consultant anaesthetist became involved and organized appropriate intensive care. After a laparotomy to exclude uterine perforation she developed multi-organ failure and died a few days later.

Had the severity of illness been recognized, experienced help would have been sought earlier. The seriousness of the mother's condition warranted better monitoring in a more appropriate environment, regardless of the sensitivities of fetal loss.

Case 15

Trainee staff cared for a patient undergoing Caesarean section because of pre-eclampsia. A consultant anaesthetist had been contacted during the Caesarean section and gave advice via the telephone but failed to attend to assess the patient or supervise the care. The patient exhibited further hypertensive changes during arousal and at this time, the anaesthetist noted that she was not tolerating the tracheal tube. After extubation she was transferred to the postoperative high dependency unit because there were no ICU beds available. Further telephone calls to the consultant anaesthetist on call only resulted in further telephone advice. Neurological changes were noted a few hours postoperatively. Intubation and transfer to the ICU occurred and there is no record to show whether control of arterial pressure during intubation was undertaken at that time either. She died without regaining consciousness.

There seems to have been no recognition of the risks of hypertensive surges during intubation or extubation. Anaesthetic care was therefore substandard. These omissions may have been due to inexperience of the trainee anaesthetist. The decision to wake and extubate this patient was probably unwise. The lack of direct consultant input into her care was substandard care. The lack of an ICU bed is further substandard care.

Whether these deficiencies caused or exacerbated the cerebral bleed is a matter of speculation. However, it is possible that had appropriate standards of care been exhibited, the outcome may have been better.

(v) Sepsis

The incidence of maternal infection during labour is in the region of 3%.[9] When septicaemia supervenes, anaesthetists should be involved in resuscitation. Additionally, sepsis can be associated with anaesthesia. The importance of constant vigilance and the use of strict asepsis during regional anaesthetic techniques cannot be overstated. These two cases illustrate possible associations between anaesthesia and sepsis.

Case 16

A primiparous woman had an uneventful spinal anaesthetic for Caesarean section because of pre-eclampsia. She developed a pyrexia on the first postpartum day and was given antibiotics. She was otherwise well until some hours later when she developed severe headache, vomiting and hypertension, and became unrousable. She was transferred to intensive care and given magnesium sulphate. Computerized tomography showed cerebral oedema. Further supportive therapy was given but her condition deteriorated and she died a few days after delivery. At post-mortem, acute purulent meningitis with sagittal sinus thrombosis was found.

This woman was appropriately treated for complications of pre-eclampsia and there was no finding of substandard care. The diagnosis of meningitis was a surprise: bacterial cultures in life and post-mortem failed to grow any organism. She had received antibiotics because of a mild pyrexia on the first postpartum day.

Although there is good epidemiological evidence that the frequency of meningitis after lumbar puncture is no greater than in the ordinary population, the possibility that causative infective or chemical agents can be introduced at spinal anaesthesia has to be recognized. The onset of symptoms is similar to two previous reports after spinal anaesthesia in obstetrics where the patients survived.[10 13] Similarly, apparently aseptic techniques had been used. Whether meningitis was caused by the spinal or was an unfortunate coincidence is impossible to say. The case highlights the need for strict asepsis during regional anaesthesia and the need to consider, as the clinicians did, other rare causes of headache which might at first be thought to be due to dural puncture or pre-eclampsia.

Case 17

Another woman developed a pyrexia of 40°C and a tachycardia of 140 beats min^{-1} after an intrauterine death. She requested and was given an epidural for analgesia for labour. She received excessive i.v. fluids to treat hypotension and developed pulmonary oedema. Disseminated intravascular coagulation developed, probably due to the intrauterine death. She became septicaemic and developed

Table 1 Key recommendations of the Editorial Board of the Confidential Enquiries into Maternal Deaths in the United Kingdom

Key recommendations
Dedicated obstetric anaesthesia services should be available in all consultant obstetric units These services should be capable of taking responsibility for regional analgesia, anaesthesia, recovery from anaesthesia and the management and monitoring of i v fluid replacement therapy
Adequate advance notice of elective high-risk cases must be given to the obstetric anaesthetic service The notice must be sufficient to allow the consultation, investigation and assembly of resources needed for these cases, to take place.
When presented with problem cases requiring special skills or investigations, obstetric anaesthetists should not hesitate to call on the assistance of anaesthetic colleagues in other subspecialties as well as colleagues in other disciplines.
Invasive central venous and arterial pressure measurement can provide vital information about the cardiovascular system which can be life saving. Invasive monitoring via appropriate routes should be used particularly when the cardiovascular system is compromised by haemorrhage or disease
Care of women at high risk of maternal haemorrhage must involve consultant obstetric anaesthetists at the earliest possible time.
Anaesthetists have a responsibility, as do all medical practitioners, to ensure that drugs are given in the correct dose, at the correct rate, by the correct route and by the most accurate means
It seems not to be widely appreciated that Syntocinon can cause profound, fatal, hypotension, especially in the presence of cardiovascular compromise
Administration should follow the guidance in the British National Formulary, Martindale and other standard formularies When given as an i v bolus the drug should be given slowly in a dose of not more than 5 iu.

multi-organ failure and had to be transferred to an ICU at another hospital where she subsequently died.

The main criticisms of this case are of the treatment of infection and the subsequent pathology. Nevertheless it is worth thinking whether the possible complications or side-effects of epidural block in a pyrexial patient were fully considered. Sympathetic blockade from epidural or spinal anaesthesia in these circumstances makes fluid and hypotension management more difficult because of impaired compensatory vasoconstriction, and capillary permeability may also be compromised. Treatment in such circumstances is difficult and requires great forethought and care.

Deaths or serious events occurring during anaesthesia

Some of the cases already described illustrate that death or serious events can occur during anaesthesia. The following cases are also included, not necessarily because there was substandard care but to reinforce the vigilance and standards required.

Case 18

A woman was known to suffer from pulmonary hypertension having had an atrial septal defect repaired many years previously. Echocardiography at 32 weeks of gestation estimated mean pulmonary artery pressures of 55 mm Hg, but it is not known if her pulmonary hypertension worsened after this. She went into labour some weeks later. Epidural analgesia was used and direct arterial and central venous monitoring were instituted. Labour failed to progress and she required a Caesarean section. She had a brief run of supraventricular tachycardia after delivery of the placenta, which spontaneously reverted to sinus rhythm but seconds later she suffered an asystolic arrest from which she could not be resuscitated. She had only received 1 iu of oxytocin.

The poor outcome from pulmonary hypertension in pregnancy is well recognized. The care of this woman was good and illustrated interdisciplinary communication and early institution of invasive monitoring. Whether the appropriate risks were communicated to the woman is important.

Case 19

A woman had a termination of pregnancy under general anaesthesia in an isolated clinic. At the end of the procedure, her oxygen saturation decreased from 98% to 83% and she became bradycardic and hypotensive. She was resuscitated with epinephrine and was intubated and ventilated. Before transfer to hospital, heavy vaginal blood loss was noticed. Fulminant DIC became apparent. She developed multiple organ failure and subsequently died.

The clinical signs were similar to those of amniotic fluid embolism. Resuscitation of this woman was prompt and emphasizes the need for experienced personnel and appropriate drugs and equipment (as recommended by the Department of Health[6]) for the rare occasions when such complications occur in isolated sites.

Case 20

A woman had an amniocentesis for a 1 in 10 risk of Down's syndrome and had a spontaneous abortion the following day. She had a general anaesthetic, delivered from a facemask, and uterine evacuation to remove remaining products of conception. There was a sudden cardiac arrest at the end of uterine evacuation. Sinus tachycardia progressed to ventricular tachycardia to asystole. Cardiopulmonary resuscitation and epinephrine were successful in restoring cardiac output. She was transferred to ICU but died several days later.

It is not clear why this lady arrested. Before the evacuation she was pyrexial, but not tachycardic or hypotensive. During anaesthesia her heart rate and arterial pressure remained normal and the cardiac arrest was sudden. This might suggest amniotic fluid embolism. If the cause of the arrest was sepsis one might postulate a myocarditis causing arrhythmia. Thereafter the picture of DIC and multi-organ failure could fit either amniotic fluid embolus or sepsis. It is unfortunate that there is apparently no histology of the lungs, uterus or heart, although it is by no means certain whether this would have been diagnostic with death occurring so long after the event. This case again illustrates the need for vigilance even for cases expected to be 'routine' or 'minor'.

The key recommendations of the Editorial Board of the Confidential Enquiries into Maternal Deaths in the United Kingdom are shown in Table 1.

References

1 Association of Anaesthetists of Great Britain and Ireland and the Obstetric Anaesthetist's Association. *Guidelines for Obstetric Anaesthetic Services* 1998

2 Ayus JC, Arieff AI. Brain damage and postoperative hyponatremia: the role of gender. *Neurology* 1996; **46**: 323–8

3 Ayus JC, Wheeler JM, Arieff AI. Postoperative hyponatremic encephalopathy in menstruant women. *Ann Intern Med* 1992; **117**: 891–7

4 Drugs used in Obstetrics, Gynaecology, and Urinary Tract Disorders. In: *British National Formulary*. Published by the British Medical Association and the Royal Pharmaceutical Society of Great Britain, 2001

5 Cicutti NJ, Smyth CE, Rosaeg OP, Wilkinson M. Oxytocin receptor binding in rat and human heart. *Can J Cardiol* 1999; **15**: 1267–73

6 Department of Health *Procedures for Approval of Independent Sector Places for the Termination of Pregnancy* 1999; 25

7 Dollery C, ed. *Therapeutic Drugs*. 2nd Edn. Edinburgh: Churchill Livingstone, 1998; 60

8 Kinsella SM, Tuckey JP. Perioperative bradycardia and asystole: relationship to vaso-vagal syncope and the Bezold–Jarisch reflex. *Br J Anaesth* 2001; **86**: 859–68

9 Lauretti GR. Infectious diseases. In: Gambling DR, Douglas MJ. *Obstetric Anesthesia and Uncommon Diseases*. Philadelphia, PA: W. B. Saunders, 1998; 333

10 Lee JJ, Parry H. Bacterial meningitis following spinal anaesthesia for Caesarean section. *Br J Anaesth* 1991; **66**: 383–6

11 Mukaddam-Daher S, Yin YL, Roy J, Gutkowska J, Cardinal R. Negative inotropic and chronotropic effects of oxytocin. *Hypertension* 2001; **38**: 292–6

12 Parfitt K, ed. *Martindale—The Complete Drug Reference*. 32nd Edn. London: Pharmaceutical Press, 1999; 1257–8

13 Roberts SP, Petts HV. Meningitis after obstetric spinal anaesthesia. *Anaesthesia* 1990; **45**. 376–7

British Journal of Anaesthesia 89 (3): 509–511 (2002)

BJA

SHORT COMMUNICATION

Effect of a single dose of esmolol on the bispectral index scale (BIS) during propofol/fentanyl anaesthesia

H. Berkenstadt[1*], R. Loebstein[2], I. Faibishenko[1], H. Halkin[2], I. Keidan[1] and A. Perel[1]

[1]Department of Anaesthesiology and Intensive Care and [2]The Institute of Clinical Pharmacology, The Chaim Sheba Medical Centre, Tel Hashomer, Israel 52621

**Corresponding author*

Background. Esmolol, a short-acting β_1-antagonist, can reduce anaesthetic requirements and decrease seizure activity during electroconvulsive therapy even after a single dose of 80 mg We studied the effect of esmolol on the bispectral index scale (BIS), which is a processed EEG recently introduced to monitor depth of anaesthesia.

Methods. We gave esmolol 80 mg to 30 healthy male patients after induction of anaesthesia using propofol, with either fentanyl (group 1) or placebo (group 2). Patients were ventilated mechanically through a laryngeal mask airway and anaesthesia was maintained using propofol to keep the BIS value between 55 and 60.

Results. Esmolol did not affect the BIS index value in either group. In group 1, the areas (mean (SD)) under the BIS vs time curve 3 min before and 3 min after esmolol administration were 145 (9) and 146 (8) respectively (P=0.116). In group 2 values were 147 (8) and 146 (7) respectively (P=0.344). In contrast, in group 1 the area under the systolic arterial pressure (SAP) curve was 299 (31) before and 270 (29) after esmolol (P<0.001), and 156 (17) and 141 (17) respectively for heart rate (P<0.001). In group 2 values were 326 (36) and 302 (41) for SAP (P<0.001) and 182 (25) and 155 (22) for heart rate (P<0.001).

Conclusions. The results suggest that a single dose of esmolol affects the SAP and heart rate but does not affect BIS values.

B J Anaesth 2002; **89**: 509–11

Keywords: anaesthesia, depth of anaesthesia; anaesthetics i.v., propofol; analgesics opioid, fentanyl; antagonists, esmolol; monitoring, bispectral index

Accepted for publication: April 22, 2002

The potentially harmful effects of autonomic nervous system activity during anaesthesia and surgery have led to the use of beta-blockers in the perioperative period.[1 2] Esmolol, a short-acting β_1-antagonist, is used to treat and prevent cardiovascular responses at this time. In addition to its effect on the sympathetic nervous system, esmolol, if given at the same time as opiates, reduces the anaesthetic requirement to suppress the response to skin incision.[3 4] Esmolol did not affect the propofol requirement for loss of responsiveness,[5] but esmolol, even in a single i.v. dose of 80 mg, reduced both clinical and EEG-detected seizure duration during electroconvulsive therapy,[6] and a single dose of epinephrine increased EEG activity.[7] As esmolol is a peripherally acting drug that does not penetrate the blood–brain barrier, the mechanism of its effects on the depth of anaesthesia and on EEG activity is not clear.

Because esmolol appears to affect EEG activity, we studied its effects by using the bispectral index scale (BIS; Aspect Medical Systems, Natick, MA, USA), which is a processed EEG recently introduced to monitor the depth of anaesthesia.[7]

Methods and results

After ethics committee approval and informed consent, we enrolled 30 male patients, aged 18–50 yr and scheduled for

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

elective knee arthroscopy. Exclusion criteria were ischaemic heart disease, hypertension, use of β-adrenergic or calcium-channel blocking drugs, second- or third-degree atrioventricular block, sinus bradycardia, chronic obstructive pulmonary disease and cardiac, renal or hepatic failure.

Patients were monitored during the study using ECG, a pulse oximeter and a capnograph. Systolic arterial pressure (SAP) was measured at 1-min intervals and heart rate (HR) was monitored continuously. The BIS (version 3.12, Aspect Medical Systems, Natick, MA, USA) was measured continuously.

On arrival in the operating room, patients were randomly assigned to one of two groups by an independent observer. Group 1 received fentanyl 2 µg i.v. and group 2 patients received placebo, in a double-blind fashion. In both groups a dose of propofol 2.5 mg kg^{-1} was followed by a continuous infusion of 5 mg kg^{-1} h^{-1}. Additional propofol was given in doses of 0.5 mg kg^{-1} to keep the BIS between 55 and 60. After insertion of a laryngeal mask airway, patients were ventilated using pressure-controlled mode with an initial pressure of 16 cm H_2O, a respiratory rate of 10, an inspiratory to expiratory ratio of 1:2 and 50% oxygen with 50% nitrous oxide. The ventilator was adjusted to keep end-tidal carbon dioxide at 28–32 mm Hg.

When SAP, HR and BIS values had been stable for 5 min, esmolol 80 mg was given in both groups and recordings were made for 3 min. During this period surgery was not allowed to progress.

The patients' age was 29 (18-49) yr in group 1 and 30 (19-50) yr in group 2 and weight was 80 (12) kg in group 1 and 81 (9) kg in group 2.

In group 1, esmolol reduced SAP from 119 (13) mm Hg to a minimum value of 105 (10) mm Hg after 2 min. In group 2 the values were 130 (16) and 120 (17) mm Hg respectively. HR decreased from 62 (7) to 55 (7) beats min^{-1} in group 1 and from 72 (10) to 61 (9) beats min^{-1} in group 2. BIS values before esmolol administration were 58 (5) in group 1 and 59 (3) in group 2. Values had not changed 3 min after esmolol administration.

Using SigmaStat software (Jadel Corporation, Access Softeck Inc., Chicago, IL, USA), the values of each variable (SAP, HR and BIS) 3 min before and 3 min after esmolol were plotted against time. The areas under the curves (AUC) before and after esmolol were then compared using a paired *t*-test.

Esmolol reduced SAP in both groups (Table 1). In group 1 the AUC for SAP *vs* time was 299 (31) before and 270 (29) after esmolol ($P<0.001$). In group 2, values were 326 (36) and 302 (41) respectively ($P<0.001$). Esmolol changed the HR. In group 1 the AUC of the HR over time was 156 (17) before esmolol, and 141 (17) after esmolol ($P<0.001$). In group 2, values were 182 (25) and 155 (22) respectively ($P<0.001$). In contrast, esmolol did not affect the BIS index. The AUC for BIS over time were 145 (9) before esmolol and 146 (8) after esmolol in group 1 ($P=0.116$), and 147 (8) and 146 (7) respectively in group 2 ($P=0.344$).

Table 1 Areas under the curve before and after esmolol administration (all values are given as mean (SD)) SAP=systolic arterial pressure (mm Hg), HR=heart rate (beats min^{-1}); BIS=bispectral index scale; AUC=area under curve (the integral of the variable over a period of 3 min)

	AUC before esmolol	AUC after esmolol	*P*
Group 1 (fentanyl, propofol)			
SAP	299 (31)	270 (29)	<0.001
HR	156 (17)	141 (17)	<0.001
BIS	145 (9)	146 (8)	0.116
Group 2 (placebo, propofol)			
SAP	326 (36)	302 (41)	<0.001
HR	182 (25)	155 (22)	<0.001
BIS	147 (8)	146 (7)	0.344

Comments

We found that a single dose of esmolol 80 mg did not affect the BIS despite the effects on HR and SAP. Previous studies found that interventions in the β-adrenergic system affect the EEG and the depth of anaesthesia. Even a single dose of esmolol 80 mg reduces seizure duration in patients undergoing electroconvulsive therapy under etomidate anaesthesia.[5] The opposite effect—increased sedation score and BIS value—was caused by a small i.v. dose (15 µg) of epinephrine.[7] The changes in EEG as well as in haemodynamic measurements in both studies were almost immediate and influenced the design of the present study. The BIS and the haemodynamic values were measured for only 3 min after esmolol administration. The lack of esmolol effect on the BIS value in the present study is not surprising as recent data show BIS suppression with an esmolol infusion, with a delay of 12–16 min between esmolol administration and the onset of half-maximal effect.[9]

How esmolol affects the depth of anaesthesia and EEG activity is unclear as the drug does not cross the blood–brain barrier. In some studies, opiates were necessary in order to achieve its effects,[4] suggesting that esmolol may affect opiate kinetics by altering cardiac function and hepatic blood flow rather than by an independent pharmacodynamic effect. In a similar way, esmolol (0.5 mg kg^{-1}) increased the onset time of rocuronium-induced muscle relaxation. The onset time was shorter after ephedrine, and the effect was attributed to the effect on cardiac output.[10] In the present study the lack of effect of esmolol on the BIS might be attributed to the dose of fentanyl (only 2 µg kg^{-1}) or to the timing of opiate administration (a few minutes before esmolol). A direct effect of esmolol, an effect of a metabolite or a secondary process are possible explanations for the change in BIS found in other studies.[9]

In conclusion, our study does not show that a single dose of esmolol affects the BIS index, even though cardiovascular effects were seen.

References

1 Mangano DT, Layug EL, Wallace A, Tated I. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. *N Engl J Med* 1996; **335**: 1713–20

2 Urban MK, Markowitz SM, Gordon MA, Urquhart BL, Kligfield P.

Postoperative prophylactic administration of beta-adrenergic blockers in patients at risk for myocardial ischemia. *Anesth Analg* 2000; **90**: 1257–61

3 Johansen JW, Flaishon R, Sebel PS. Esmolol reduces anaesthetic requirement for skin incision during propofol/nitrous oxide/morphine anesthesia. *Anesthesiology* 1997; **86**: 364–71

4 Johansen JW, Schneider G, Windsor AM, Sebel PS. Esmolol potentiates reduction of minimum alveolar isoflurane concentration by alfentanil. *Anesth Analg* 1998; **87**: 671–6

5 Orme R, Leslie K, Umranikar A, Ugoni A. Esmolol and anesthetic requirement for loss of responsiveness during propofol anesthesia. *Anesth Analg* 2002, **94**: 112–6

6 Van den Broek WW, Leentjens AF, Mulder PG, Kusuma A, Bruijn JA. Low-dose esmolol bolus reduces seizure duration during electroconvulsive therapy: a double blind, placebo-controlled study. *Br J Anaesth* 1999; **83**: 271–4

7 Andrzejowski J, Sleigh JW, Johnson IA, Sikiotis L. The effect of intravenous epinephrine on the bispectral index and sedation. *Anaesthesia* 2000, **55**: 761–3

8 Johansen JW, Sebel PS. Development and clinical application of electroencephalographic bispectrum monitoring. *Anesthesiology* 2000; **93**: 1336–44

9 Johansen JW. Esmolol promotes electroencephalographic burst suppression during propofol/alfentanil anesthesia. *Anesth Analg* 2001; **93**: 1526–31

10 Szmuk P, Ezri T, Chelly JE, Katz J. The onset time of rocuronium is slower by esmolol and accelerated by ephedrine. *Anesth Analg* 2000; **90**: 1217–9

British Journal of Anaesthesia 89 (3) 512–14 (2002) BJA

CASE REPORTS

Flow-by induced hypoventilation in high spinal cord lesions—report of two cases[†]

S. Kannan[1], N. Sherwood[2]* and A. Armfield[2]

[1]Department of Anaesthetics and [2]Department of Nursing, City Hospital, Dudley Road, Birmingham B18 7QH, UK

**Corresponding author*

Flow triggering in ventilators is an alternative to pressure triggering. Differences between these two trigger mechanisms may not be clinically significant in most patients. We report two patients with high spinal cord lesions in whom the use of flow triggering was unsuccessful. Severe muscle weakness in these patients made them sensitive to small changes in ventilator trigger characteristics.

Br J Anaesth 2002; **89**: 512–14

Keywords: complications, quadriplegia; lung, tidal volume; ventilation, hypoventilation; ventilation, mechanical

Accepted for publication: March 28, 2002

During mechanical ventilation, change from expiration to inspiration can be time cycled, or triggered by pressure or flow changes.[1] Whereas time cycling is independent of patient activity, pressure and flow triggering require the patient to start the breath[1]. For a pressure-triggered breath, the ventilator detects the patient's effort as a decrease in pressure. The decrease in pressure required to trigger the ventilator is set by the clinician.[2] For a flow-triggered breath, the ventilator senses patient effort from changes in inspiratory flow caused by the patient.[2] Flow-triggering and flow-by technology was introduced in the Puritan Bennett 7200 ventilators (Puritan Bennett Corporation, USA) to reduce the delay between the patient's inspiratory effort and the supply of gas to the patient during assisted ventilation.[3] The ventilator delivers a predetermined flow of gas (base flow) into the patient circuit before inspiration. The ventilator detects flow to the patient as the difference between the delivered flow and the flow leaving at the expiratory valve. The operator determines the inspiratory flow necessary to trigger a breath (flow sensitivity). When the difference between the delivered and the expiratory flow increases to this amount, then the ventilator triggers to inspiration. The default flow sensitivity setting in these ventilators is 3 litre min^{-1}. In flow-by mode pressure triggering is thus replaced by flow triggering. We report two cases where using flow-by caused failure to trigger, which was reversed when the flow-by was stopped. There have been no similar reports in the literature.

Case reports

Case 1

A 66-yr-old man was being mechanically ventilated for respiratory failure after traumatic quadriplegia caused by fracture of the odontoid peg. The neck was stabilized by cervical traction by a Halo apparatus. The patient was conscious and no sedative agents were being given. There was loss of sensation to touch, pain, and temperature below C3 dermatome. Motor power was absent in all the limbs. Cranial nerves were intact.

The ventilator (Puritan Bennett 7200) settings were as follows: continuous positive airway pressure mode with pressure support 16 cm H_2O, pressure sensitivity 0.5 cm H_2O, positive end expiratory pressure 7.6 cm H_2O, and fraction of inspired oxygen concentration 0.35. On these settings, the tidal volume was about 0.32 litre, ventilatory frequency 25 min^{-1} and minute ventilation around 8.0 litre min^{-1}. The patient was unable to trigger the ventilator if the pressure sensitivity was set to 1 cm H_2O. To assess the ability of the patient to trigger the ventilator with flow triggering, flow-by was started with the default base flow of 5 litre min^{-1} and flow sensitivity of 3 litre min^{-1}. The patient's respiratory rate decreased to 14 min^{-1} while the tidal volume, oxygen saturation, and cardiovascular meas-

---

[†] This article is accompanied by Editorial II

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

urements remained the same. The patient did not appear to be uncomfortable and there were no accessory muscle movements to suggest that the patient was unsuccessfully attempting to trigger the ventilator. An error in the flow-by settings was suspected, and the ventilator was set to the original settings. The respiratory rate returned to 25 min^{-1}. The decrease in respiratory rate was considered to be caused by an inadequate base flow. Therefore, the base flow was increased to 10 litre min^{-1} and flow-by was re-started, but the same phenomenon occurred again, and persisted when the base flow was increased to 20 litre min^{-1}. The flow sensitivity was not altered during these changes in base flow settings. The ventilator was then returned to the original settings.

Case 2

A 34-yr-old man mechanically ventilated for respiratory failure caused by pneumonia. In the past, he had undergone total pancreatectomy for chronic pancreatitis. He was an insulin-dependant diabetic and had a history of recurrent multiple abscesses in various parts of his body. Ten days later, when he was being weaned from the ventilator, it was noticed that the patient was unable to move his limbs. He was conscious and not sedated. A computerized tomographic scan of the neck showed an epidural abscess at the C2–4 level. Clinically, there was no sensation to touch, pain, or temperature below C4 dermatome. There was no movement in his limbs. Cranial nerves were not involved. Before admission to the intensive care unit, there had been no clinical evidence of this epidural abscess.

The ventilator settings were continuous positive airway pressure mode with pressure support of 18 cm H_2O, pressure sensitivity of 0.5 cm H_2O, positive end expiratory pressure of 5 cm H_2O and fraction of inspired oxygen concentration of 0.35. With these settings, the tidal volume was around 0.48 litre, ventilatory frequency 18 min^{-1}, and minute ventilation was 9.4 litre min^{-1}. When flow-by was started with a default base flow of 5 litre min^{-1} and flow sensitivity of 3 litre min^{-1}, the tidal volume remained the same but the ventilatory frequency decreased to 8 min^{-1}. On decreasing the flow sensitivity to 1 litre min^{-1}, the ventilatory frequency increased to 15 min^{-1} and the tidal volumes were 0.49 litre. When the base flow was increased to 10 litre min^{-1} and flow sensitivity was increased to 5 litre min^{-1}, the patient could not trigger the ventilator but weak respiratory efforts were seen. The ventilator was re-set to pressure sensitivity settings and flow-by was abandoned.

Discussion

Inspiratory efforts can be insufficient to trigger the ventilator in some patients.[4] Factors which can affect this can be either ventilator related (high resistance, leaks, high base flow) or patient related (weakness, flail chest, intrinsic positive end expiratory pressure).[5] The current ventilators are sensitive enough to allow a patient to trigger with minimum of effort. Studies comparing the efficacy of flow triggering *vs* pressure triggering have shown equivocal results.[5] While some have shown flow triggering to be superior, others have found either minimal difference or pressure triggering to be better.[1 2 6 7] The differences between pressure and flow triggering were not related to the trigger used but to the ventilatory support programming with each trigger.[2 7] More recent ventilators have corrected this difference so that the inspiratory work of breathing is similar with the two modes of triggering.[5 6 8]

It is likely that the high spinal lesion in these patients caused some diaphragmatic weakness. Indeed, the second patient had decreased diaphragmatic movements on ultrasonography. Therefore, these patients were extremely sensitive to small changes in trigger settings. Using flow sensitivity of 3 litre min^{-1} made it more difficult for the patient to trigger the ventilator. Trigger pressure (the maximum pressure decrease at the beginning of an inspiratory effort) and pressure time product on flow sensitivity settings of 2 and 3 litre min^{-1} lies between pressure sensitivity settings of 0.5 and 1 cm H_2O.[2] The second patient could trigger the ventilator on a flow sensitivity setting of 1 litre min^{-1}. It is likely that the first patient could have responded in the same way. Although in many patients the minor differences between pressure and flow triggering and the various settings of flow triggering may not be clinically significant,[6] this may not be so in patients with quadriplegia who rely on their feeble muscle strength to trigger the ventilator.

One of the risks of very high sensitivity settings is triggering by movements caused by cardiac activity.[9] Although this did not happen here, it should be kept in mind especially if patients have a hyperdynamic circulation. A further hazard with flow-by settings needs to be considered. In Puritan Bennett 7200 ventilators, flow-by is automatically inactivated during nebulization and needs to be manually switched on again if the mode is to continue. For this reason, flow-by was abandoned in the second patient even though he could trigger the ventilator with a flow sensitivity of 1 litre min^{-1}.

To summarize, we describe two patients with quadriplegia from high spinal cord lesions where the flow-by mode led to hypoventilation. In patients with extensive muscle weakness, the ability to trigger the ventilator can be affected by small changes in trigger sensitivity. The default flow sensitivity settings in flow-by mode may not be sufficient for such patients to successfully trigger the ventilator.

References

1 Sassoon CS, Gruer SE. Characteristics of the ventilator pressure- and flow-trigger variables. *Intensive Care Med* 1995; **21**: 159–68

2 Goulet R, Hess D, Kacmarek RM. Pressure vs flow triggering during pressure support ventilation. *Chest* 1997; **111**. 1649–53

3 Puritan Bennett Ventilator Manual. 22335 A 1–92 Option 50 (release 2.0), 1–8

4 Chao DC, Scheinhorn DJ, Stearn-Hassenpflug M. Patient-ventilator trigger asynchrony in prolonged mechanical ventilation. *Chest* 1997; **112**: 1592–9

5 Hill LL, Pearl RG. Flow triggering, pressure triggering, and autotriggering during mechanical ventilation. *Crit Care Med* 2000; **28**: 579–81

6 Aslanian P, El Atrous S, Isabey D, *et al.* Effects of flow triggering on breathing effort during partial ventilatory support. *Am J Resp Crit Care Med* 1998; **157**: 135–43

7 Polese G, Massara A, Poggi R, Brandolese R, Brandi G, Rossi A. Flow-triggering reduces inspiratory effort during weaning from mechanical ventilation. *Intensive Care Med* 1995; **21**: 682–6

8 Tutuncu AS, Cakar N, Camci E, Esen F, Telci L, Akpir K. Comparison of pressure- and flow-triggered pressure-support ventilation on weaning parameters in patients recovering from acute respiratory failure. *Crit Care Med* 1997; **25**: 756–60

9 Imanaka H, Nishimura M, Takeuchi M, *et al.* Autotriggering caused by cardiogenic oscillation during flow-triggered mechanical ventilation. *Crit Care Med* 2000; **28**: 402–7

British Journal of Anaesthesia **89** (3): 514–17 (2002)

Posterior spinal ligament rupture associated with laryngeal mask insertion in a patient with undisclosed unstable cervical spine

C. J. Edge[1] *, N. Hyman[2 3], V. Addy[1], P. Anslow[4], C. Kearns[1], R. Stacey[5] and C. Waldmann[6]

[1]Nuffield Department of Anaesthetics, Oxford Radcliffe Hospitals Trust, Oxford, UK. [2]Department of Neurology, Royal Berkshire Hospital, Reading, UK. [3]Department of Neurology, Oxford Radcliffe Hospitals Trust, Oxford, UK. [4]Department of Radiology, Oxford Radcliffe Hospitals Trust, Oxford, UK. [5]Department of Neurosurgery, Oxford Radcliffe Hospitals Trust, Oxford, UK. [6]Department of Anaesthetics, Royal Berkshire Hospital, Reading, UK

**Corresponding author: The Stone Barn, Gravel Lane, Drayton OX14 4HY, UK*

A case of posterior spinal ligament rupture associated with a general anaesthetic for a laparoscopic cholecystectomy is reported. The role of the general anaesthetic in this case is discussed and a review of the literature is presented.

Br J Anaesth 2002; **89**: 514–17

Keywords: ligament, posterior spinal; complications, ligament rupture; equipment, masks anaesthesia

Accepted for publication: April 18, 2002

Airway management may cause problems in patients with cervical spine pathology. According to prevailing dogma, direct laryngoscopy is hazardous in the presence of cervical instability. Direct laryngoscopy causes superior rotation of the occiput and C1 in the sagittal plane and mild inferior rotation of C3–C5,[1 2] while tracheal intubation causes slight additional superior rotation at the occiput and C1. There is minimal movement below C3 during direct laryngoscopy.[1 3] However, the amount of movement in the cervical spine from C3 to C7 remains difficult to determine. One study[4] examined the movements of the C5–C6 joint before and after surgical destabilization in cadavers and showed a difference of less than 2 mm translation and 4° of angulation between the stable and unstable specimens at direct laryngoscopy. Another radiographic study[5] of unstable spines showed that other airway manoeuvres, such as jaw thrust, caused similar degrees of movement. Several authors have therefore advocated alternative methods of airway management in cases of potential cervical spine instability,[6–15] all of which may be associated with technical or operator complications.

The laryngeal mask airway (LMA[†][1]) has been advocated 'to fill the gap between the tracheal tube and the face mask'. Brimacombe and colleagues[16] reviewed the advantages and disadvantages of the LMA and found that the LMA is, in general, easier to place and better tolerated than the tracheal

---

[†] LMA® is the property of Intavent Limited.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

tube. However, neurovascular morbidity has been recorded with the LMA. Hypoglossal,[17] lingual[18 19] and recurrent laryngeal[20] nerve injuries have been noted and occlusion of the lingual artery[21] leading to tongue cyanosis has also been recorded, but we have been unable to find any reports of spinal cord problems associated with the use of the LMA.

We describe the case of a patient who developed tetraplegia during surgery due to unrecognized instability of the cervical spine despite the fact that direct laryngoscopy was not used. We discuss the reasons for this occurrence.

Case report

A 64-yr-old man was admitted for elective laparoscopic cholecystectomy for gallstones, having had the operation postponed on two previous occasions for non-medical reasons. He noted a history of pain in the region of his right shoulder, which his general practitioner had ascribed to referred pain from his gall bladder exacerbated by stress. He admitted to occasional pain in his neck, which he said caused him no problems. His medical history included an appendicectomy complicated by peritonitis, diet-controlled diabetes mellitus, and osteoarthritis for which he had undergone knee arthroscopy. He denied any other medical problems.

At induction he was given midazolam, propofol, fentanyl and atracurium and a size 5 LMA was inserted. The insertion of the LMA was described as straightforward by the anaesthetist and did not involve any untoward movements of the neck or jaw thrust. The ultimately successful surgery was complicated by the presence of adhesions and lasted for 75 min. The lowest non-invasive systolic blood pressure recorded during the anaesthetic was 100 mm Hg. The LMA was removed with jaw opening but without head movement in recovery. The patient complained of abdominal pain, for which he was treated with opiate and a non-steroidal anti-inflammatory drug. He was transferred to the ward after 30 min. At no time during or after the operation was the patient's neck flexed or extended.

Approximately 1 h after the patient had been returned to the ward it was noted that he had difficulty in moving his legs and there was no sensation to pain or touch in his abdomen. A weak cough was noted but there was good air entry into the lungs bilaterally. Shortly thereafter he was seen by a consultant neurologist, who noted no movement in the legs and weakness of elbow extension together with weakness of the left arm distally. The level of sensation to pinprick was C5/6 on both sides with poor joint position sense in his left little finger. Joint position and vibration sense was absent in both legs. The patient was managed with a cervical collar and urinary catheterization, and an MRI scan was performed. A consultant neuroradiologist reported these images as showing a rupture of the posterior spinal ligament with haematoma cord compression. The disc was not protruding. The patient was admitted to ITU where methylprednisolone 3 g was given over 15 min. He was then transferred to the regional neurological centre, where he underwent C5/6 discectomy with insertion of a wedge of bone. At operation, a completely ruptured and very oedematous posterior spinal ligament was found at the site. Since that time the patient has made little recovery and he remains effectively tetraplegic. He has undergone further uncomplicated surgery for small bowel obstruction due to herniation of bowel through a hole in the mesentery.

After the laparoscopic cholecystectomy, the patient's wife admitted that the patient had visited his general practitioner on the day before surgery as he was experiencing weakness in his legs and had had some difficulty in walking. He was also suffering from severe neck pain, necessitating him sleeping upright on the night before surgery in a chair. However, there was no history of trauma to the neck. He had failed to inform the anaesthetist of these facts, as he was worried that his surgery would again be cancelled.

Discussion

A combination of mechanical deformation and vascular compromise of the cervical spine is thought to be necessary for the development of myelopathy. It is believed that the duration of these unfavourable conditions is a crucial factor. Animal models[22 23] indicate that ≥6 h of constriction of dogs' spinal cords leads to permanent loss of function, whilst after constriction for ≤1 h there is nearly complete recovery. In our case, the time from induction to waking was of the order of 90 min in total but, from the history obtained after cholecystectomy, some compromise of the cervical spinal cord had occurred before the operation. There is evidence that cord injury can occur in cases in which the malposition of the spine is very slight.[24–26] In our case, neck manipulation as a result of direct laryngoscopy or insertion of the LMA cannot be blamed. The insertion of the LMA would have caused very little movement of the neck, as it did not require jaw thrust or hyperflexion or extension of the neck to position the LMA satisfactorily. Loss of muscle tone owing to administration of muscle relaxant would, however, have increased the likelihood of further damage to an already abnormal cervical spine.

Hypotension[27] can cause cervical cord damage even in normal patients. In our patient, the use of the laparoscope and carbon dioxide for insufflation of the abdomen would reduce venous return and hence cardiac output, although there is evidence that blood pressure increases during laparoscopic cholecystectomy.[28–30] Additionally, an increase in the spinal and epidural venous pressure would increase the cerebrospinal fluid pressure, causing a decrease in the spinal arterial perfusion pressure. No periods of hypotension were observed throughout the course of the operation, but in the case of this patient the blood flow to the cervical spine might have been compromised as a result of the surgical technique. Some workers[31] believe that an element of induced hypertension may be beneficial but this view must be tempered as animal work has indicated that increased oedema and haemorrhage of the cord are a possibility.[32]

Rupture of the posterior longitudinal ligament (PLL) in the cervical spine is also reported as a consequence of accidental trauma to the neck. Hyperflexion of the cervical spine can cause injury to the middle column of the spine (consisting of the posterior vertebral body, the posterior longitudinal ligament and the posterior annulus fibrosus) together with the posterior column of the spine (consisting of the posterior elements of the spine, the ligamentum flavum, the interspinous ligaments, the supraspinous ligament and the facet joint capsules). Hyperextension causes injury to the anterior column of the spine (consisting of the anterior vertebral body, the anterior longitudinal ligament and the anterior annulus fibrosus) and the middle column.[33] However, another process by which rupture of the PLL may occur is in conjunction with hypertrophy and ossification of the PLL.[34] Interestingly, glucose intolerance is a risk factor for ossification of the PLL in Japanese men[35] and our patient had diet-controlled diabetes mellitus.

This case serves to highlight the fact that any degree of neck manipulation in a patient with an unstable cervical spine may be hazardous.

References

1 Sawin PD, Todd MM, Traynelis VC, *et al.* Cervical spine motion with direct laryngoscopy and orotracheal intubation. *Anesthesiology* 1996, **85**: 26–36

2 Mackart DJJ, Bhagwanjee S, van der Merwe R. Spinal cord injury as a result of endotracheal intubation in patients with undiagnosed cervical spine fractures. *Anesthesiology* 1997; **87**: 418–20

3 Horton WA, Fahy L, Charters PL. Disposition of cervical vertebrae, atlanto-axial joint, hyoid and mandible during X-ray laryngoscopy. *Br J Anaesth* 1989; **63**: 435–8

4 Donaldson WF III, Towers JD, Doctor A, Brand A, Donaldson VP. A method to evaluate motion of the unstable spine during intubation techniques. *Spine* 1993; **14**: 2020–3

5 Aprahamian C, Thompson BM, Finger WA, Darin JC. Experimental cervical spine injury model: evaluation of airway management and splinting techniques. *Ann Emerg Med* 1984; **13**: 584–7

6 Hastings RH, Marks JD. Airway management for trauma patients with potential cervical spine injuries. *Anesth Analg* 1991; **73**: 471–82

7 Wood PR, Lawler PGP. Managing the airway in cervical spine injury. *Anaesthesia* 1992; **47**: 792–7

8 Bivins HG, Ford S, Bezmalinovic Z, Price HM, Williams JL. The effect of axial traction during orotracheal intubation of the trauma victim with an unstable cervical spine. *Ann Emerg Med* 1988; **17**: 25–9

9 Crosby ET, Lui A. The adult cervical spine: implications for airway management. *Can J Anaesth* 1990; **37**: 77–93

10 American College of Surgeons Committee on Trauma. *Advanced Trauma Life Support Program for Doctors* Chicago. American College of Surgeons, 1997

11 Danzl, DF, Thomas DM. Nasotracheal intubations in the emergency department. *Crit Care Med* 1980; **8**: 677–82

12 Delaney KA, Hessler R. Emergency flexible fibreoptic nasotracheal intubation: a report of 60 cases. *Ann Emerg Med* 1988; **17**: 919–26

13 Iserson KV. Blind nasotracheal intubation. *Ann Emerg Med* 1981; **10**: 468–71

14 Mlinek EJ, Clinton JE, Plummer D, Ruiz E. Fibreoptic intubation in the emergency department *Ann Emerg Med* 1990; **19**: 359–62

15 Meschino A, Devitt JH, Koch JP, Szalai JP, Schwartz ML. The safety of awake tracheal intubation in cervical spine injury. *Can J Anaesth* 1992; **39**: 114–7

16 Brimacombe JR, Berry AM, White PF. The laryngeal mask airway: limitations and controversies. *Int Anesthesiol Clin* 1998; **36**: 155–82

17 Nagai K, Sakuramoto C, Goto F. Unilateral hypoglossal nerve paralysis following the use of the laryngeal mask airway. *Anaesthesia* 1994; **49**: 603–4

18 Ahmad NS, Yentis SM. Laryngeal mask airway and lingual nerve injury. *Anaesthesia* 1996; **51**: 707–8

19 Laxton CH, Kipling R. Lingual nerve paralysis following the use of the laryngeal mask airway. *Anaesthesia* 1996; **51**: 869–70

20 Lloyd Jones FR, Hegab A. Recurrent laryngeal nerve palsy after laryngeal mask airway insertion. *Anaesthesia* 1996; **51**. 171–2

21 Wynn JM, Jones KL. Tongue cyanosis after laryngeal mask insertion. *Anesthesiology* 1995; **82**. 787–8

22 Dolan EJ, Tator CH, Endrenyi L. The value of decompression for acute experimental spinal cord compression injury. *J Neurosurg* 1980; **53** 749–55

23 Delamarter RB, Sherman J, Carr JB. Pathophysiology of acute spinal cord injury. Recovery after immediate and delayed decompression. *J Bone Joint Surg* 1995; **77A**. 1042–9

24 Deem S, Shapiro HM, Lawrence F, Marshall LF. Quadriplegia in a patient with cervical spondylosis after thoracolumbar surgery in a patient in the prone position. *Anesthesiology* 1991; **75**: 527–8

25 Linstedt U, Maier C, Joehnk H, Stephani U. Threatening spinal cord compression during anesthesia in a child with mucopolysaccharidosis VI. *Anesthesiology* 1994; **80**: 227–9

26 Bejjani GK, Rizkallah RG, Tzortidis F, Mark AS. Cervical spinal cord injury during cerebral angiography with MRI confirmation: case report. *Neuroradiology* 1998; **40**: 51–3

27 Singh U, Silver JR, Welply NC. Hypotensive infarction of the spinal cord. *Paraplegia* 1994; **32**: 314–22

28 Joris JL, Noirot DP, Legrand MJ, Jacquet NJ, Lamy ML. Haemodynamic changes during laparoscopic cholecystectomy. *Anesth Analg* 1993; **76**: 1067–71

29 Critchley LA, Critchley JA, Gin T. Haemodynamic changes in patients undergoing laparoscopic cholecystectomy: measurement by transthoracic electrical bioimpedance. *Br J Anaesth* 1993; **70**: 681–3

30 Walder AD, Aitkenhead AR Role of vasopressin in the haemodynamic response to laparoscopic cholecystectomy. *Br J Anaesth* 1997; **78**: 264–6

31 Vale FL, Burns J, Jackson AB, Hadley MN. Combined medical and surgical treatment after acute spinal cord injury: results of a prospective pilot study to assess the merits of aggressive medical resuscitation and blood pressure management. *J Neurosurg* 1997; **87**: 239–46

32 Guha A, Tator CH, Rochon J. Spinal cord blood flow and systemic blood pressure after experimental spinal cord injury in rats. *Stroke* 1989; **20**: 372–7

33 Benedetti PF, Fahr LM, Kuhns LR, Hayman LA. MR imaging findings in spinal ligamentous injury. *Am J Roentgenol* 2000; **175**: 661–5

34 Kondo S, Onari K, Watanabe K, Hasegawa T, Toguchi A, Mihara H. Hypertrophy of the posterior longitudinal ligament is a

prodromal condition to ossification: a cervical myelopathy case report. *Spine* 2001; **26**: 110–4

35 Shingyouchi Y, Nagahama A, Niida M. Ligamentous ossification of the cervical spine in the late middle-aged Japanese men. Its relation to body mass index and glucose metabolism. *Spine* 1996; **21**: 2474–8

British Journal of Anaesthesia **89** **(3)**: 517–19 (2002)

Complete airway obstruction in a ventilated patient after oesophageal dilatation

S. Francis, W. C. Russell* and J. P. Thompson

Department of Anaesthesia, Critical Care and Pain Management, Leicester Royal Infirmary, University Hospitals Leicester, Leicester LE1 5WW, UK

**Corresponding author*

A case of instrumental perforation of the oesophagus is presented. This caused systemic sepsis, requiring tracheal intubation and positive pressure ventilation. Sudden unexpected life-threatening airway obstruction was caused by distal tracheal compression by a peritracheal abscess. The aetiology and management of distal tracheal obstruction is discussed.

Br J Anaesth 2002; **89**: 517–19

Key words: airway, obstruction; complications, mediastinitis; gastrointestinal tract, oesophagus

Accepted for publication: April 4, 2002

Circumferential compression of the trachea is very unusual, having been reported previously in the presence of mediastinal tumours.[1] It can cause complete lower airway obstruction and is usually insidious in onset. Tracheal compression by mediastinitis has not to our knowledge been described. This case report describes this condition and illustrates the rapid onset.

Case report

A 68-yr-old female presented with dysphagia and an enlarged submandibular lymph node. She underwent oesophagoscopy, pharyngoscopy and laryngoscopy, and excision biopsy of the lymph node. The procedure was uneventful, but the next day she developed surgical emphysema involving the upper chest and neck. A gastrograffin swallow showed a leak of radiographic contrast from the upper oesophagus but the exact location was unclear. A nasogastric tube was passed. She was not given any oral intake and the nasogastric tube was used for free drainage. Treatment with cefuroxime and metronidazole was started. Over the next 48 h she became dyspnoeic and hypoxic. Her ventilatory frequency was 20–25 min^{-1} and an FI_{O_2} of 0.5 was required to maintain a Sa_{O_2} greater than 90%. Chest x-ray showed bilateral basal lung collapse and consolidation.

Her respiratory function deteriorated (Pa_{O_2} 9.6 kPa, FI_{O_2} 1.0) and she was transferred to the intensive care unit for tracheal intubation and artificial ventilation. She developed systemic sepsis, which was considered to be caused by a hospital-acquired pneumonia. Epinephrine and dobutamine were started to maintain her arterial pressure and urine output. A pulmonary artery flotation catheter was sited, and the initial measurements were: cardiac output was 5.8 litre min^{-1}, systemic vascular resistance was 797 dyne s^{-1} cm^{-5}, pulmonary artery capillary wedge pressure was 20 mm Hg, and central venous pressure was 10 mm Hg.

She received artificial ventilation with BIPAP (bilevel positive airway pressure) with an inspiratory pressure (P_{insp}) of 24 cm H_2O and PEEP (positive end expiratory pressure) of 5 cm H_2O. Therapy with ciprofloxacin was commenced in addition to cefuroxime and metronidazole. Daily chest x-rays revealed persistent changes in both bases, but no suggestion of mediastinal collection.

On the tenth postoperative day a sudden decrease in minute volume with reduced delivered tidal volume was noted. Initially it was thought that the tracheal tube might have been dislodged or displaced against the tracheal wall or

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

above the vocal cords. A bougie was inserted through the tracheal tube and the tube advanced further down to 24 cm from the lips. Because ventilation improved, a check laryngoscopy was not performed and other diagnoses, such as tension pneumothorax seemed unlikely. However, shortly afterwards difficulties recurred with inadequate ventilation despite increasing the inspiratory airway pressure.

An urgent fibreoptic bronchoscopy was done, where it was seen that the tracheal tube had moved back to the original position of 22 cm and the trachea was swollen and inflamed with complete circumferential occlusion at that level. The tracheal rings were not visible, the posterior tracheal wall was bulging at 24 cm, and the carina looked swollen with marked oedema. The tracheal tube was advanced to just above the carina, which allowed satisfactory ventilation with the previous airway pressures.

A chest x-ray now showed widening of the upper mediastinum. A contrast-enhanced CT scan (Fig. 1) showed a large low attenuation lesion containing pockets of gas seen in the prevertebral region of the neck and upper chest, extending on either side of the trachea from the superior cornua of the thyroid to the carina. The oesophagus and trachea were displaced anteriorly.

The features were consistent with inflammatory changes in the neck and upper chest, and bilateral basal consolidation and pleural effusion. It was decided that surgical drainage was indicated because of sepsis and tracheal compression. She had a right thoracotomy with drainage of the mediastinal abscess and both pleural effusions. Drains were placed in both pleural spaces and the superior and inferior mediastinum (32F).

Her gas exchange remained poor.

A tracheostomy was performed on day 14 to improve weaning and over the next 3 weeks her condition improved. All the drains except one of the mediastinal drains were removed. After 24 days of intensive care she was transferred to the ENT ward. Total oesophagectomy was considered, but with conservative treatment a controlled oesophago-cutaneous fistula developed. Her condition gradually improved. After a further 2 months she was able to eat and mobilize, and was discharged home.

Discussion

Instrumental perforation of the oesophagus was followed by a peritracheal abscess, causing sudden, unexpected life-threatening airway obstruction. Circumferential compression of the trachea is very unusual, having been reported previously in the presence of mediastinal tumours,[1] but not to our knowledge with mediastinitis.

Oesophageal perforation can occur spontaneously with vomiting or retching, or after instrumentation. It is estimated that the incidence is approximately 1 in 100 rigid oesophagoscopies.[2] The commonest early symptoms are acute chest pain, epigastric pain, and dyspnoea. Signs include surgical emphysema, or signs of pneumothorax or mediastinal air. The diagnosis is usually confirmed with chest x-ray and contrast swallow.

The management of oesophageal perforation depends on the level and size of the perforation.[2] With instrumental perforations this is usually conservative, with complete fasting, nasogastric suction, and broad-spectrum antibiotics, if the diagnosis is made before mediastinal contamination

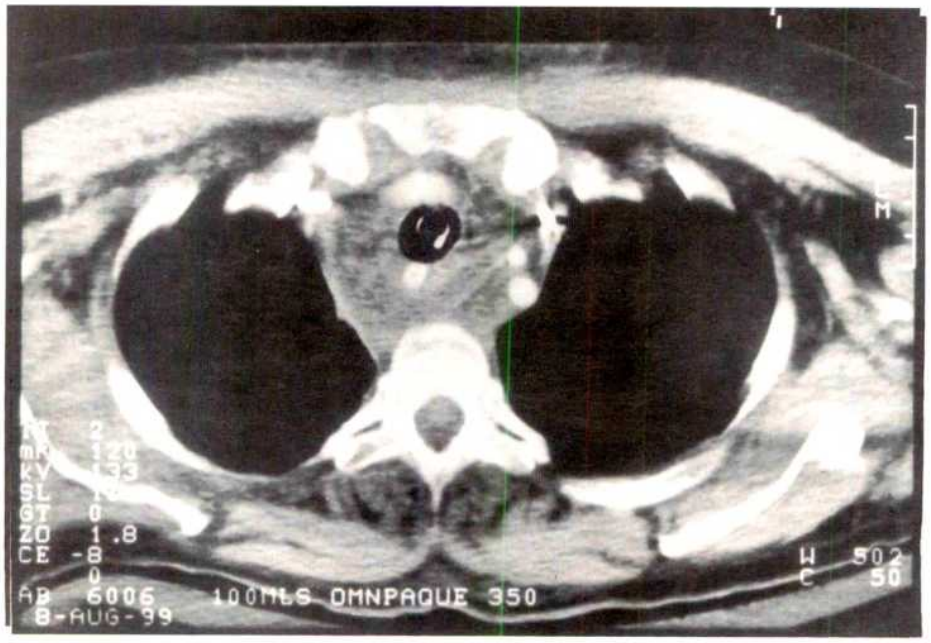


Fig 1 A contrast-enhanced CT scan demonstrated a large low attenuation lesion containing pockets of air seen in the prevertebral region of the neck and upper chest. The trachea is held open by the tracheal tube.

has occurred [3 4] Surgery is indicated for large free lower oesophageal perforations[4] or complications, for example mediastinitis.[5] In the case reported here, the exact level of perforation was not clear but was in the upper oesophagus, and she initially progressed satisfactorily with conservative treatment. Signs of systemic sepsis developed, with respiratory failure and cardiovascular instability. At that stage, she was thought to have developed a nosocomial pneumonia, but we were concerned that a mediastinal infection may be developing.

The sudden onset of airway obstruction was first thought to be related to problems with the tracheal tube position. After recurrence of the obstruction, it became clear that this was caused by extrinsic tracheal compression, which occurred suddenly when the extrinsic intrathoracic pressure reached a level that caused the trachea to collapse. Artificial ventilation with BIPAP, where P_{insp} was constant, meant that once the extrinsic pressure exceeded the P_{insp}, the ventilation became ineffective. In addition, the mediastinal abscess had probably been developing for a few days, causing some inflammation and weakening of the tracheal wall. The chest x-ray appearances did not change during this period, and the tracheal tube was effectively stenting the upper trachea, so the possibility of sudden airway obstruction was unsuspected.

This case shows that life-threatening distal tracheal obstruction can occur suddenly, and may be undetected by serial chest x-rays. Furthermore, the obstruction developed despite an appropriately positioned tracheal tube. Conventional teaching is that if a tracheal tube is obstructed it should be removed, but in this case, removal of the tube is likely to have made ventilation more difficult or impossible.

During the conservative management of oesophageal perforation, the threshold for performing a CT scan of the chest should be low. In this case, earlier imaging would probably have shown the mediastinal collection, and allowed drainage before the subsequent airway obstruction occurred. However, the index of suspicion was not high and although CT scanning was considered, her poor cardiorespiratory state made us reluctant to move her for a chest CT scan.

An alternative could have been regular inspection of the trachea and carina by fibreoptic bronchoscopy, although this carries risks in an unstable patient, and it is unclear at what stage early tracheal inflammation or compression would have been detectable.

We suggest that in a patient with mediastinal pathology, the possibility of airway obstruction should always be considered, even in the presence of an appropriately placed tracheal tube. Intensive care patients are very often dependent on PEEP and high F_{IO_2}, and investigation may be difficult. The axiom of changing a tracheal tube first in the setting of acute airway obstruction is not always safe. In this case, fibreoptic bronchoscopy was very useful to determine the cause, and plan subsequent management.

References

1 Robie DK, Gursoy MH, Pokorny WJ. Mediastinal tumours—airway obstruction and management. *Semin Paed Surg* 1994; **3**: 259–66
2 Smith CCK, Tanner NC. The complications of gastroscopy and oesophagoscopy. *Br J Surg* 1956; **43**: 396–403
3 Shaffer HA, Valezuela G, Mittal RK. Esophageal perforation. A reassessment of the criteria for choosing medical or surgical therapy. *Arch Int Med* 1992; **152**· 757–61
4 Lyons SL, Seremetis MG, deGuzman VC, Peabody JW Ruptures and perforations of the esophagus: the case for conservative management. *Ann Thoracic Surg* 1978, **25** 344–50
5 Triggiani E, Belsey R. Oesophageal trauma· incidence, diagnosis, and management. *Thorax* 1977; **32**: 241–49

British Journal of Anaesthesia 89 (3) 519–23 (2002)

Coronary artery spasm and non-Q-wave myocardial infarction following intravenous ephedrine in two healthy women under spinal anaesthesia

A. Wahl[1], F. R. Eberli[1], D. A. Thomson[2] and M. Luginbühl[2*]

[1]Cardiology, Swiss Cardiovascular Centre and [2]Department of Anaesthesiology, University Hospital of Bern, CH-3010 Bern, Switzerland

**Corresponding author*

Vasovagal episodes occur frequently in young healthy patients undergoing venous cannulation and loco-regional anaesthesia. We report two cases of severe coronary vasospasm and non-Q-wave infarction in healthy young women after administration of ephedrine for vasovagal

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

symptoms at the onset of spinal anaesthesia. In the light of unopposed vagal predominance predisposing patients to coronary vasospasm, even in young healthy patients, atrophine and not ephedrine should be the first line treatment for bradycardia with or without hypotension under spinal anaesthesia.

Br J Anaesth 2002; **88**: 519–23

Keywords: agonists, adrenergic; complications, hypertension; heart, arrhythmia, tachycardia; spinal cord, sensory block; veins, complications

Accepted for publication: May 14, 2002

Vasovagal reactions may occur in 10% of patients, and have an even higher incidence in patients under 40 yr of age and in those with a prior history.[1] Vasovagal syncope induced by anaesthetic interventions may occur in 1 in 5000 cases.[2] Vagal predominance is considered to be an important risk factor for the development of severe bradycardia or asystole during spinal anaesthesia,[3] and it may also induce multivessel coronary vasospasm that resolves after administration of atropine.[4] To prevent asystole, Pollard[3] suggests a stepwise treatment for bradycardia under spinal anaesthesia using atropine, ephedrine and then epinephrine, whereas Kinsella and Tuckey[5] consider ephedrine as the most logical treatment. Ephedrine or related alkaloids have induced coronary artery spasms with or without myocardial infarctions in several cases,[6–12] some of them fatal. Three other cases were related to administration of ephedrine in the context of regional anaesthesia,[13–15] all of them in male subjects of more than 40 yr, one of whom had a history of cocaine abuse.

We describe two cases of coronary artery spasm induced by ephedrine given for treatment of a vasovagal reaction at the placement of a spinal anaesthetic in young women who had minimal cardiovascular risk factors and angiographically normal coronary arteries.

Case 1

A 26-yr-old athletic female (height, 169 cm; weight, 72 kg) was scheduled for pelvic osteotomy under combined spinal–epidural anaesthesia. She admitted to smoking (four cigarettes month^{-1}) but otherwise she had no risk factors for cardiovascular disease. After oral premedication with 7.5 mg of midazolam and an i.v. injection of 50 μg of fentanyl to this slightly nervous patient, the epidural space was located with an 18-gauge Tuohy needle in the third lumbar interspace with the patient in the sitting position. Thereafter, 20 mg of plain bupivacaine was injected intrathecally after dural puncture with a 27-gauge Pencan™ needle (Braun, Melsungen, Germany) through the epidural needle. During subsequent placement of the epidural catheter for postoperative analgesia, the patient complained suddenly of nausea and dizziness, while the patient's arterial pressure decreased from 145/85 to 125/50 mm Hg and her heart rate from 80 to 55 beats min^{-1}. Presuming a rapidly increasing level of spinal block and aiming at completing the fixation of the inserted epidural catheter in the sitting patient, 10 mg of ephedrine followed by 0.5 mg of atropine and another 10 mg of ephedrine were given intravenously within a few minutes. Then the patient was placed supine. Shortly afterwards, ECG monitoring showed a non-sustained wide complex regular rhythm at a rate of 150 beats min^{-1} consistent with ventricular tachycardia, followed by sinus tachycardia at 195 beats min^{-1}, ST-segment elevation and arterial hypertension (215/150 mm Hg). The patient complained of chest pain and dyspnoea, although her heart rate and arterial pressure returned to normal within 5–10 min. Immediately after this event, the level of spinal anaesthesia was at T8. Surgery was cancelled, and the patient taken to the postanaesthesia care unit for cardiology consultation.

The ECG 1 h after the event showed diffuse ST-segment depression, and transthoracic echocardiography revealed a moderately-to-severely impaired left ventricular systolic function (ejection fraction 40%), with mild mitral regurgitation, akinesia of the basal segments and apical hypercontractility. The ECG had returned to normal 8 h later, whereas the troponin-I concentration rose from 4.7 μg litre^{-1} (2.5 h after the event) to a peak of 29.5 μg litre^{-1} 8 h later (normal range <0.6). Total CK and CK-MB mass peaked at 268 units litre^{-1} (normal range <167) and 18.9 μg litre^{-1} (normal range <4.0), respectively, 11 h after the event, consistent with non-Q-wave myocardial infarction. Coronary angiography performed the next day revealed normal coronary arteries. Global left ventricular systolic function was normal (EF 64%), but hypokinesia of the anterobasal, inferobasal and lateral wall segments was noted, and left ventricular end diastolic pressure was increased (22 mm Hg). An echocardiography performed on the 4th day showed normalization of left ventricular systolic function, with a small pericardial effusion. The patient underwent uneventful surgery under general anaesthesia 3 months later.

Case 2

A 34-yr-old female (height, 163 cm; weight, 66 kg) with a history of smoking (7 pack-years) and a family history of coronary artery disease, was scheduled for left hip arthrotomy under combined spinal–epidural anaesthesia. She had experienced a vasovagal syncopal episode during blood donation, and had undergone prior uneventful spinal anaesthesia for knee arthroscopy 2 yr earlier. Thirty minutes after oral premedication with 7.5 mg of midazolam, the obviously anxious patient was monitored with ECG, non-invasive arterial pressure and pulse oximetry. A 14-gauge i.v. cannula was inserted under local anaesthesia. After injection of 50 μg of fentanyl intravenously, the patient was moved to the sitting position for epidural puncture, when she suddenly complained of nausea and dizziness. The patient was immediately placed supine and felt better. She was then turned to the right lateral position and again complained of nausea and was pale and bradycardic (38 beats min^{-1}). Two doses of ephedrine 5 mg were administered intravenously together with 500 ml of lactated Ringer's solution both to treat the bradycardia and to provide prophylaxis against the expected sympathetic block with spinal anaesthesia. The subsequent dural puncture in the third lumbar interspace, intrathecal injection of 20 mg bupivacaine and placement of the epidural catheter were uneventful. The intravascular position of the catheter was excluded by injection of 3 ml of 2% mepivacaine with epinephrine 5 μg ml^{-1} after a negative aspiration test. The patient was turned to the supine position for placement of a Foley catheter and an additional 500 ml of pentastarch was infused. Ten minutes later a sensory level of T3 was reached without a significant decrease of arterial pressure or heart rate. The patient was again turned to the right lateral position for surgery. Immediately afterwards she became pale, dizzy and nauseated, her arterial pressure decreased from 110/65 to 75/40 mm Hg and her heart rate from 70 to 35 beats min^{-1}. Aiming at correcting both heart rate and arterial pressure three 5 mg boluses of ephedrine were injected, which was followed by a non-sustained wide complex regular rhythm at 150 beats min^{-1} consistent with ventricular tachycardia, spontaneously converting to sinus tachycardia at 170 beats min^{-1} with ST-segment elevation. At that time the patient was hypertensive (230/135 mm Hg), and showed progressive desaturation to 90% associated with crackles on auscultation of the depending right chest, chest pain, dyspnoea and headache. At this stage a total of 1000 ml of lactated Ringer's solution and 500 ml of pentastarch had been infused. Her heart rate and arterial pressure returned to normal within 5 min but oxygen saturation did not improve significantly during the subsequent 15 min. Surgery was cancelled and the patient moved to the post anaesthesia care unit.

The ECG 90 min after the event showed ST-segment depression in V3 and V4, but the chest x ray showed cardiomegaly and right-sided pulmonary oedema. Echocardiography revealed a slightly diminished left ventricular systolic function (EF 55%), with akinesia of the basal segments and apical hypercontractility, and moderate mitral regurgitation. Troponin-I and total CK concentration peaked at 25.8 μg litre^{-1} and 185 units^{-1}, respectively, 10 h after the event, consistent with minimal non-Q-wave myocardial infarction. Coronary angiography performed the next day revealed normal coronary arteries. The left ventricular systolic function was slightly depressed (EF 50%) with hypokinesia of the anterobasal, inferobasal and lateral wall segments, and the left ventricular end diastolic pressure was increased (22 mm Hg). An echocardiography performed on the 4th day showed normalization of left ventricular systolic function, with only minimal mitral regurgitation. The patient underwent uneventful surgery under general anaesthesia 3 months later. The correct ephedrine concentration was confirmed by the hospital pharmacy in the remainder of the liquid from the 'ephedrine syringe' used in this patient and the possibility of contamination with other substances was excluded.

Discussion

We observed two cases of chest pain, dyspnoea, non-sustained ventricular tachycardia, ST segment depression, non-Q-wave infarction and extended myocardial stunning occurring immediately after i.v. administration of ephedrine to treat symptomatic hypotension and bradycardia, after induction of spinal anaesthesia in two young women with angiographically normal coronary arteries. Both patients presented with vagal symptoms prior to the administration of the neuraxial block.

In Case 1 the sitting position was maintained for a few minutes in order to complete epidural catheter fixation despite the patient's complaint of nausea and dizziness. The decrease of heart rate and arterial pressure was aggressively treated with ephedrine assuming a rapidly increasing level of spinal block. However, the level of the block recorded immediately after the event was only T8. She was not hypotensive and only slightly bradycardic at the onset of symptoms, although her heart rate decrease from 80 to 55 beats min^{-1} was abrupt. Many of the reported cases of asystole under spinal anaesthesia occurred within seconds of the abrupt onset of bradycardia, suggesting a cardiac reflex induced by an acute drop in right-sided cardiac filling pressure.[16 17] Because of this and another case report,[18] the early use of ephedrine is recommended ('treat the downward trend') in our department. In retrospect this patient's symptoms were more likely to have been vasovagal in origin and the dose of ephedrine excessive The use of the sitting position for easier siting of combined spinal–epidural analgesia may have further increased the risk of a vasovagal episode.[5]

In Case 2, a clearly anxious patient with a history of vasovagal syncope and some vasovagal reaction even before the start of the procedure, exhibited a rather high level of spinal block that was well tolerated until she was turned to a lateral position. In contrast to the first patient, she was administered a larger volume of i.v. fluid and kept in the right lateral position for at least 15 min after the onset of symptoms. This explains why the subsequent pulmonary oedema was predominantly on the right side. As in the first patient the initial symptoms of fainting were treated first with ephedrine and not atropine. Nevertheless, the patient developed severe bradycardia and hypotension on moving her from the supine to the right lateral position.

We can only speculate as to the pathophysiological mechanism causing myocardial ischaemia, diastolic dysfunction, pulmonary oedema and infarction associated with the transient regional left ventricular dysfunction. A predominant vagal tone, as occurred in both of our patients, may induce multivessel coronary vasospasm.[4] A decreased sympathetic tone caused ST-segment depression in women during Caesarean section under spinal anaesthesia.[19] Intracoronary injection of acetylcholine is used as a diagnostic test to identify patients with coronary artery spasm, which supports the pathogenic role of predominant vagal tone.[20 21] In a recent study on dobutamine stress echocardiography[22] the pure β-stimulator, dobutamine, induced coronary vasospasm in patients with coronary spastic angina inducible by intracoronary acetylcholine.

Other explanations are less likely. Myocardial ischaemia secondary to a massively increased oxygen demand associated with sinus tachycardia and severe hypertension after administration of atropine and ephedrine is unlikely. In young patients with excellent exercise tolerance and angiographically normal coronary arteries, such periods of hypertension, even when preceded by hypotension, are usually well tolerated and have not been reported to be associated with regional wall abnormalities. Even less likely as an explanation would be acute thrombus formation in normal coronary arteries with spontaneous lysis, since the regional distribution of the stunned myocardium would require several coronary arteries to be affected.

Anaesthetists are more and more reluctant to use vagolytic drugs prophylactically, in order not to mask the tachycardia induced by accidental i.v. injection of an epinephrine-containing test dose, and also because the tachycardia induced by atropine is considered potentially harmful in elderly patients. Moreover vasovagal syncope occurring during placement of i.v. lines or regional blocks is considered a harmless and mostly spontaneously resolving event. Vasovagal fainting is associated with an increased vagal, and a decreased sympathetic, activity explaining bradycardia and hypotension, respectively.[5] Kinsella and Tuckey[5] therefore suggest ephedrine as the logical first-line drug treatment of bradycardia during spinal anaesthesia, whereas others recommend atropine first and then ephedrine.[3]

In order to prevent fatal cardiac arrest under spinal anaesthesia early aggressive treatment of bradycardia and hypotension with fluids, atropine, ephedrine and eventually epinephrine is recommended. How early, at what dose and what intervals the drugs are to be administered must be decided by the attending anaesthetist. Whereas administering 'too little, too late' may lead to asystole, 'too much, too early' may lead to arrhythmia and coronary vasospasm with infarction, as in our two cases. Furthermore, although the ephedrine doses as administered in our patients seem to be large, similar doses were investigated for prophylactic use without serious side effects.[23 24]

The important parasympathetic predominance in two young, anxious women may have increased the risk for coronary vasospasm that was then induced by, retrospectively, too large a dose of ephedrine, administered under the assumption of a rapidly increasing level of spinal block. Prior administration of atropine, especially to the first patient who was not hypotensive at the onset of the symptoms, might have prevented the coronary vasospasm.

We conclude that a delay of immediate supine placement of a patient suffering from vasovagal symptoms during placement of neuraxial block in the sitting position may not be compensated by increasing the dose of α- and β-adrenergic drugs. In the light of unopposed vagal predominance predisposing to coronary vasospasm, even in young healthy patients, the previously suggested sequence of first injecting atropine and then ephedrine in the case of bradycardia with or without hypotension under spinal anaesthesia is further corroborated.

Acknowledgement

This work was funded by the research funds of the Cardiology and Anaesthesia Department, University Hospital of Bern, Switzerland.

References

1 Pavlin DJ, Links S, Rapp SE, Nessly ML, Keyes HJ. Vaso-vagal reactions in an ambulatory surgery center. *Anesth Analg* 1993; **76**: 931–5

2 Hosie L, Wood JP, Thomas AN. Vasovagal syncope and anaesthetic practice. *Eur J Anaesthesiol* 2001; **18**: 554–7

3 Pollard JB. Cardiac arrest during spinal anesthesia: common mechanisms and strategies for prevention. *Anesth Analg* 2001; **92**: 252–6

4 Osborn LA, Reynolds B. Vagally mediated multivessel coronary artery spasm during coronary angiography. *Cathet Cardiovasc Diagn* 1998; **44**: 423–6

5 Kinsella SM, Tuckey JP. Perioperative bradycardia and asystole: relationship to vasovagal syncope and the Bezold–Jarisch reflex. *Br J Anaesth* 2001; **86**: 859–68

6 Wiener I, Tilkian AG, Palazzolo M. Coronary artery spasm and myocardial infarction in a patient with normal coronary arteries: temporal relationship to pseudoephedrine ingestion. *Cathet Cardiovasc Diagn* 1990; **20**: 51–3

7 Derreza H, Fine MD, Sadaniantz A. Acute myocardial infarction after use of pseudoephedrine for sinus congestion. *J Am Board Fam Pract* 1997; **10**: 436–8

8 Cockings JG, Brown M. Ephedrine abuse causing acute myocardial infarction. *Med J Aust* 1997; **167**. 199–200

9 Theoharides TC. Sudden death of a healthy college student related to ephedrine toxicity from a ma huang-containing drink [letter]. *J Clin Psychopharmacol* 1997; **17**: 437–9

10 Franklin QJ. Sudden death after typhoid and Japanese encephalitis

vaccination in a young male taking pseudoephedrine. *Mil Med* 1999; **164**: 157–9

11 Adverse events associated with ephedrine-containing products—Texas, December 1993–September 1995. *Morb Mortal Wkly Rep* 1996; **45**: 689–93

12 Josefson D. Herbal stimulant causes US deaths. *Br Med J* 1996; **312**: 1378–9

13 Lustik SJ, Chhibber AK, van Vliet M, Pomerantz RM. Ephedrine-induced coronary artery vasospasm in a patient with prior cocaine use. *Anesth Analg* 1997; **84**: 931–3

14 Hirabayashi Y, Saitoh K, Fukuda H, Mitsuhata H, Shimizu R. Coronary artery spasm after ephedrine in a patient with high spinal anesthesia. *Anesthesiology* 1996; **84**: 221–4

15 Imamura M, Matsukawa T, Kashimoto S, Nonaka A, Kumazawa T. A case of coronary artery spasm during spinal anesthesia. *J Clin Anesth* 1996; **8**: 522–4

16 Lovstad RZ, Granhus G, Hetland S. Bradycardia and asystolic cardiac arrest during spinal anaesthesia: a report of five cases. *Acta Anaesthesiol Scand* 2000; **44**: 48–52

17 Geffin B, Shapiro L. Sinus bradycardia and asystole during spinal and epidural anesthesia: a report of 13 cases. *J Clin Anesth* 1998; **10**: 278–85

18 Bailey PL. Sinus arrest induced by trivial nasal stimulation during alfentanil–nitrous oxide anaesthesia. *Br J Anaesth* 1990; **65**: 718–20

19 Eisenach JC, Tuttle R, Stein A. Is ST segment depression of the electrocardiogram during cesarean section merely due to cardiac sympathetic block? *Anesth Analg* 1994; **78**: 287–92

20 Goto A, Ito S, Kondo H, *et al.* Evaluation of adjunctive intracoronary administration of acetylcholine following intravenous infusion of ergonovine to provoke coronary artery spasm. *J Cardiol* 1999; **34**: 309–16

21 Sueda S, Ochi N, Kawada H, *et al.* Frequency of provoked coronary vasospasm in patients undergoing coronary arteriography with spasm provocation test of acetylcholine. *Am J Cardiol* 1999; **83**: 1186–90

22 Kawano H, Fujii H, Motoyama T, Kugiyama K, Ogawa H, Yasue H. Myocardial ischemia due to coronary artery spasm during dobutamine stress echocardiography. *Am J Cardiol* 2000; **85**: 26–30

23 Kee WD, Khaw KS, Lee BB, Lau TK, Gin T. A dose-response study of prophylactic intravenous ephedrine for the prevention of hypotension during spinal anesthesia for cesarean delivery. *Anesth Analg* 2000; **90**: 1390–5

24 Chan WS, Irwin MG, Tong WN, Lam YH. Prevention of hypotension during spinal anaesthesia for caesarean section. ephedrine infusion versus fluid preload. *Anaesthesia* 1997; **52**: 908–13

British Journal of Anaesthesia **89** (3) 524–9 (2002)

Correspondence

Hirudin and its reversal

Editor—I read the informative editorial on heparin resistance by Anderson and Saenko[1] with interest. However, experience forces me to point out a possible area for confusion. Currently, there is no drug reversal available for r-hirudin and reversal of its anticoagulant effect relies entirely on renal elimination (biological half-life of 1–1.5 h).[2] In patients with poor renal function, r-hirudin has a prolonged half-life, which may lead to serious bleeding problems after cardiopulmonary bypass (CPB)[3] Indeed, poor renal function can prolong the half-life of r-hirudin to 30 h, and end-stage renal failure can prolong it to more than 300 h. There may be little change with dialysis.[4]

Although haemofiltration used in conjunction with CPB is an established procedure and can be useful in accelerating the elimination of r-hirudin, some filter membranes will eliminate only 15–42% of the circulating drug.[5] Given that r-hirudin has a molecular weight of less than 7000 Da and most filters have a pore size of 50 000 Da, this is unsurprising R-hirudin will penetrate most filters in either direction—from plasma to ultrafiltrate and back again. The wide variation in membrane clearance rates presumably relates to the electrostatic charge on the membrane

I was the anaesthetist responsible for a 71-year-old, 64-kg man with proven type II heparin-induced thrombocytopenia who required urgent coronary artery bypass grafting. Despite nearly normal preoperative serum creatinine (117 µmol litre^{-1}), his preoperative glomerular filtration rate was only 41 ml min^{-1}. A haemofiltration line was electively placed pre-bypass. In spite of careful monitoring of the hirudin level and ecarin clotting time, the measured r-hirudin level was 2 1 µg ml^{-1} (CPB therapeutic level 2.5–4 µg ml^{-1}) after bypass. During the first four postoperative hours, blood loss was 1500 ml h^{-1}. Haemofiltration (Baxter PSHF 1200) was instituted to little clinical effect. Samples taken from the circuit pre- and post-membrane showed a pre-filter hirudin level of 1.1 µg ml^{-1} and a post-filter level of 0.95 µg ml^{-1}. In total, the patient required 41 units of packed red cells, six pools of platelets, 17 units of fresh frozen plasma and 32 units of cryoprecipitate. Over 16 h after it was last administered, the hirudin level finally fell to below 0 4 µg ml^{-1} and the patient produced clots. He went on to make an otherwise uneventful recovery.

In contrast to the above-described scenario, plasmapheresis filters (pore size 15 000 Da) can eliminate as much as 60–70% of circulating r-hirudin.[6] Unfortunately, they will also remove large quantities of plasma proteins, including procoagulants, and this in turn may require the administration of quantities of fresh frozen plasma as a replacement

R. I. P. Dornan
Edinburgh
UK

Editor—We read with interest the problems encountered in Dr Dornan's patient who required emergency coronary bypass grafting, and in whom a diagnosis of type II heparin-induced thrombocytopenia had been made. With a preoperative reduced creatinine clearance, potential complications were clearly anticipated with the elective siting of a haemofiltration line, although subsequent haemodialysis (Baxter PSHF 1200) appeared to have little effect on the r-hirudin level. Although the r-hirudin level was within a therapeutic range for bypass, there was a clear need for reversal of the antithrombotic action of the drug, in view of bleeding complications

Hirudin is a highly potent and specific inhibitor of thrombin which inactivates thrombin through the formation of an almost irreversible complex.[7] Recombinant hirudin, available since 1997, exhibits tenfold less avid affinity for thrombin than leech-derived hirudin. Nevertheless, a potential weakness of r-hirudin remains the lack of an effective antidote in the event of bleeding. In such situations, r-hirudin can be eliminated by haemofiltration, and high-flux dialysis membranes appear to be the 'treatment of choice'; the key to the successful removal of hirudin lies in choosing the correct membrane.[5] Some low-flux membranes are only partially permeable to r-hirudin, while membranes made from polysulphone or regenerated cellulose have been shown to be impermeable to r-hirudin.[8]

Other direct thrombin inhibitors exist with some practical advantages over r-hirudin; bivalirudin, a hirulog, is a synthetic thrombin inhibitor that causes merely transient inhibition of thrombin. Its mechanism of action is unique and involves its conversion into a low affinity inhibitor after binding to the active site of thrombin.[9] With only a small proportion of bivalirudin undergoing clearance by the kidneys, and with its shorter half-life, this drug may be a practical alternative to r-hirudin in the future, particularly in patients with renal impairment. Likewise, melagatran, a non-covalent inhibitor of the active site of thrombin, may also be a promising alternative[10]

J. A. M Anderson
E. L. Saenko
Belfast
UK

1 Anderson JAM, Saenko EL. Heparin resistance *Br J Anaesth* 2002; **88** 467–9

2 Nowak G, Bucha E, Goock T, *et al.* Pharmacology of r-hirudin in renal impairment. *Thromb Res* 1992; **66**: 707–15

3 Koster A, Kuppe H, Hetzer R, Mertzlufft F. Bleeding complications associated with r-hirudin application for cardiopulmonary bypass in patients with heparin-induced thrombocytopenia type II *Anesth Analg* 1999; **88**· SCA3

4 Vanholder R, Camez A, Veys N, *et al* Pharmacokinetics of recombinant hirudin in haemodialyzed end-stage renal failure patients *Thromb Haemost* 1997; **77**: 650–5

5 Frank RD, Farber H, Stefanidis I, Lanzmich R, Kierdorf HP. Hirudin elimination by haemofiltration. a comparative *in vitro* study of different membranes. *Kidney Int Suppl* 1999, **72**· S41–5

6 Koster A, Merkle F, Hansen R, *et al.* Elimination of recombinant hirudin by modified ultrafiltration during simulated cardiopulmonary bypass: assessment of different filter systems. *Anesth Analg* 2000; **91**: 265–9

7 Weitz JI, Hirsh J. New anticoagulant drugs *Chest* 2001; **119**: 95S–107S

8 Bucha E, Kreml R, Nowak G. *In vitro* study of r-hirudin permeability through membranes of different haemodialysers. *Nephrol Dial Transplant* 1999; **12** 2922–6

9 Marganore JM, Bourdon P, Jablonski J, Ramachandran KL, Fenton JW. Design and characterisation of hirulogs: a novel class of bivalent peptide inhibitors of thrombin. *Biochemistry* 1990; **29** 7095–7101

10 Bredberg U, Eriksson U, Taure K, Johansson L, Frison L, Gustafsson D. Effects of melagatran, a novel direct thrombin inhibitor, in healthy volunteers following intravenous, subcutaneous and oral administration. *Blood* 1999; **94** Abstract 110 28a

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Platelet function assessment in Glanzmann's thrombasthenia

Editor—We read with interest the case report by Monte and Lyons[1] about the peripartum management of a patient with Glanzmann's thrombasthenia. The report displays how a multidisciplinary approach to a complicated case can aid in its successful management.

We agree that the thromboelastographic picture of Glanzmann's thrombasthenia has not been reported before. An aspect of the authors' discussion that we would like to challenge is their comment that there is no accepted or universally available monitor of platelet function. The PFA-100™ system is a platelet function analyser designed to measure platelet-related primary haemostasis It has been in use since the mid-1990s.[2] In principle, citrated whole blood is aspirated through a capillary into an aperture, the surface of which is coated with collagen to which ADP or epinephrine is added. The time taken for the aperture to occlude by formation of a primary haemostatic plug is measured—this is the closure time.

Extensive work has been carried out to validate the PFA-100™ in many different patient groups, including patients on antiplatelet agents, patients undergoing cardiopulmonary bypass, and uraemic and cirrhotic patients. A clinical sensitivity of 94.9% and specificity of 88.8% has been found with the PFA, compared with 94.3% and 88.3%, respectively, for platelet aggregometry tests.[3] The PFA has been found to be highly reliable in identifying congenital thrombocytopathies, including Glanzmann's thrombasthenia.[4]

The test is simple, rapid (giving a result within 5 min), and does not require specialist training. Use of the PFA is becoming increasingly widespread and it is now a well-accepted monitor of platelet function in both Europe and North America.

W. Marchant
S. Mallet
London
UK

Editor—We thank Marchant and Mallett for their interest in our case report, and are pleased that they only have one point of criticism

TEG® measures platelet function in terms of clot strength, determined by the firmness of the fibrin/platelet matrix. The PFA-100™ system measures the ability of platelets to plug a hole in a membrane in terms of closing time. The two tests are complementary. It would have been particularly interesting to see what the PFA would have made of the rFVII, since this would have probably answered the question of its efficacy in this condition. Unfortunately, the nearest PFA that we are aware of is the one in Dr Mallett's hospital.

These and other points of care platelet function monitors are reviewed by Harrison,[5] and for further information the reader is directed to his review.

S. Monte
G. Lyons
Leeds
UK

1 Monte S, Lyons G Peripartum management of a patient with Glanzmann's thrombasthenia using Thrombelastograph®. *Br J Anaesth* 2002; **88**· 734–38

2 Kundu SK, Hellmann EJ, Sio R, Garcia C, Davidson RM, Ostgaard RA. Description of an *in vitro* platelet function analyser – PFA-100. *Semin Thromb Haemost* 1995; **21**. 106–12

3 Mammen EF, Comp PC, Gosselin R, *et al.* PFA-100™ System: A new method for assessment of platelet dysfunction. *Semin Thromb Haemost* 1998, **24**: 195–202

4 Muller M, Becker-Hagendorf K, Westrup D, Seifried E, Kirchmaier CM. PFA-100™ system: A sensitive screening test for platelet-related hemostasis defects. *Ann Haematol* 1997; **74**: 72

5 Harrison P. Progress in the assessment of platelet function *Br J Haematol* 2000; **111**. 733–44

Cerebrovascular carbon dioxide reactivity in children anaesthetized with sevoflurane

Editor—We read with interest the article on cerebrovascular carbon dioxide reactivity (CCO$_2$R) in children anaesthetized with sevoflurane.[1] We have a few comments regarding the article.

(i) In the first paragraph, the authors have mentioned that controlled hyperventilation acts through the mechanism of CCO$_2$R to reduce both cerebral blood flow and cerebral blood volume. However, it is not proven what causes the changes in cerebral blood flow velocity and cerebral blood volume following changes in arterial carbon dioxide tension (Pa_{CO_2})

(ii) In the discussion, the authors mention that carbon dioxide exerts a rapid and considerable influence on the cerebral circulation by dilating cerebral arterioles and increasing the cerebral circulation. The authors have not given any reference to this statement. There are studies showing the effect of different tensions of arterial carbon dioxide on the diameter of cerebral vessels of different sizes,[2–5] by measuring the vascular diameter rather than assuming the change in the diameter of these vessels on the basis of changes in flow measured by transcranial Doppler sonography.

(iii) The investigators have insonated the rather large M1 segment of the middle cerebral artery, but made conclusions about changes in diameter of much smaller distal arteries.

(iv) Are the speculated changes in the middle cerebral artery diameter (derived from changes in flow velocity) real changes or the effect of pulsatility[6] as a result of changes in cardiovascular haemodynamics?

(v) All volatile anaesthetics depress myocardial function, which may affect cardiac output, and in turn affect cerebral flow and cerebral flow velocity.

(vi) Changes in Pa_{CO_2} lead to dramatic changes in cardiac output,[5] which also influence the cerebral blood flow and cerebral blood flow velocity.

(vii) Should we assume that changes in cerebral blood flow, cerebral blood velocity and cerebral blood volume are due to changes in the diameter of the cerebral vessels? Or are these changes due to changing cardiac output and flow velocity in the central circulation?

(viii) The authors have recorded an increase in cerebral blood flow velocity following an increase in PE'_{CO_2}. They mention that these changes were not the result of 'cardiovascular alterations' (heart rate and mean arterial pressure were stable throughout the study period). Cardiovascular alterations do not merely include changes in heart rate and mean arterial pressure More important variables are cardiac output, stroke volume and peripheral vascular resistance, which were not measured.

The authors cannot contribute the recorded changes in flow velocity to arterial dilatation since they have not measured arterial diameter Others have shown that cerebral arterial diameter down to 0.57 mm is unchanged when Pa_{CO_2} varies from 28 to 80 mm Hg.[5]

F. A. Brohi
H. G Djurberg
Riyadh
Saudi Arabia

Editor—Thank you for the opportunity to reply to Drs Brohi and Djurberg. The aim of the opening statement in our introduction is to define the clinical relevance of the investigation. The term cerebrovascular reactivity to carbon dioxide (CCO$_2$R) describes the observed effect which Pa_{CO_2} has on cerebral blood flow and cerebral blood volume. The manipulation of this phenomenon is a cornerstone of neuroanaesthetic practice.

The aim of the study was to determine the effects of sevoflurane on CCO$_2$R, by measuring middle cerebral artery blood flow velocity (CBFV) at different levels of PE'_{CO_2} by transcranial Doppler (TCD) sonography. We did not set out to investigate, nor did we postulate the underlying mechanism. However, we cited the work of Severinghaus and Lassen who demonstrated that a change in Pa_{CO_2} caused a rapid change in cerebral blood flow. They postulated that this was most likely due to an effect on arteriolar tone caused by a change in extracellular pH resulting from rapid diffusion of carbon dioxide from the arterial blood into arteriolar smooth muscle.

We gave a detailed explanation of the methodology and possible sources of error associated with TCD sonography. We did not set out to measure, nor did we make any conclusions about, changes in the diameter of the middle cerebral artery or any other cerebral blood vessels However, we did state that relative changes in cerebral blood flow velocity have been shown to correlate well with changes in cerebral blood flow measured by intravenous xenon^{133} clearance and radioactive microspheres In order for this to be true, the cross-sectional area of the M1 segment of the MCA must not alter significantly with changes in blood pressure, Pa_{CO_2}, or the use of anaesthetic agents. This has been verified by direct measurement during craniotomy, and using both angiography and Doppler signal power analysis.

We agree that volatile anaesthetics depress myocardial function, which may affect cardiac output, and in turn may affect cerebral flow and cerebral flow velocity. Furthermore, we discussed the direct effects which sevoflurane has been shown to have on the cerebral vasculature. The aim of the study was to investigate the effect of a constant 1.0 MAC sevoflurane on CCO$_2$R.

We agree that a change in Pa_{CO_2} has complex effects on haemodynamics including heart rate, cardiac output, stroke volume, blood pressure and systemic vascular resistance. We did not set out to investigate, nor did we comment on their influence on CCO$_2$R However, we did observe that heart rate and mean blood pressure remained remarkably stable throughout the study period, which suggests that the observed changes in CBFV were not a result of cardiovascular alteration.

We did not set out to elucidate the mechanism underlying the phenomenon of CCO$_2$R nor did we attribute the observed changes in cerebral blood flow velocity to arterial dilatation. However, we did state that having accounted for all of the confounding factors that could affect the CBFV and the possible measurement errors, one can conclude that the observed changes in CBFV are attributable to changes in PE'_{CO_2}.

D. A. Rowney
Edinburgh
UK

1 Rowney DA, Fairgrieve R, Bissonnette B. Cerebrovascular carbon dioxide reactivity in children anaesthetized with sevoflurane. *Br J Anaesth* 2002; **88**: 357–61

2 Huber P, Handa J. Effect of contrast material, hypercapnia, hyperventilation, hypertonic glucose and papaverine on the diameter of cerebral arteries. *Invest Radiol* 1967; **2**: 17–32

3 Bradac GB, Simon RS, Heidsieck CH. Angiographically verified transient alterations of the intracranial arteries and veins in dependence on different CO$_2$ tensions. *Neuroradiology* 1976; **10** 257–62

4 Giller CA, Bowman G, Dyer H, Mootz L, Krippner W Cerebral arterial diameter during changes in blood pressure and carbon dioxide during craniotomy. *Neurosurgery* 1993, **12**: 737–42

5 Djurberg HG, Seed RF, Price Evans DA, *et al* Lack of effect of CO$_2$ on cerebral arterial diameter in man. *J Clin Anesth* 1998; **10**: 646–51

6 Lindegaard KF. Indices of pulsatility. In: Newell DW and Aaslid R, eds *Transcranial Doppler.* New York: Raven Press Ltd, 1992; 67–82

Ventilating in recovery—the way forward: intensive therapy or critical care?

Editor—Having read the editorial in the *BJA*,[1] we have a number of concerns regarding the widespread adoption of the post-operative critical care unit (POCCU) as a solution to critical care bed shortages. What the authors have demonstrated is that simply increasing the total number of critical care beds in the Royal Liverpool University Hospitals from 13 to 17 produced entirely predictable reductions in cancelled operations.

The most recent Department of Health review of critical care services (Comprehensive Critical Care[2]) emphasized the importance of classifying critically ill patients on the basis of their dependency (i.e care required), rather than the location where they were being nursed (e.g. ICU, HDU, POCCU, etc.). The authors admit that their present ICU is constrained by architectural factors and so they have merely expanded their Level 2 or 3 care into the recovery area.

Unfortunately, the authors have missed this point when they claim that the 'establishment of a critical care facility in the operating theatre may have advantages over ITU expansion'. The POCCU beds are indeed critical care beds and are just one solution to the common problem of ICU bed shortage. A number of equally effective solutions exist and hospitals must choose one that suits their needs the best. Our concern about POCCUs and overnight intensive recovery (OIR) is that, although they may manage Level 2 and 3 patients, they may not comply with the standards pertaining to architecture, equipment, facilities and manpower that are required to care for critically ill patients The standards required are well established,[3] and it is clear from the editorial that the POCCU may not meet some of these important standards.

In summary, the authors have described a possible solution, but part of its success may simply reflect the fact that the number of critical care beds has been increased. POCCUs may be a retrospective step because the standards required to care for Level 3 patients may not be met. This is something that the specialties of anaesthesia and intensive care should avoid simply for the sake of expediency.

S. Ridley
P. Nightingale
Norwich
UK

Editor—Thank you for the opportunity to reply to Ridley and Nightingale. We are disappointed with their concerns about the postoperative critical care unit (POCCU) or overnight intensive recovery (OIR) approach to managing surgical patients. As they say 'hospitals must choose the [solution] which suits their needs the best'. The editorial tried to demonstrate that intensive therapy unit (ITU) expansion may not be the most appropriate response.

Our APACHE II data show consistently higher scores for the ITU than the POCCU each month (mean data for April 1, 2001 to

September 30, 2001: ITU 15.3, POCCU 12.6). This suggests that a different patient population is being cared for on the POCCU. The reduction in cancelled operations may not be due to the increase in critical care beds alone. Some of these patients may have had their operation but gone to a surgical HDU and not the ITU, in the days before we opened the POCCU. The opening of the POCCU has therefore also allowed more appropriate use of surgical HDU beds. We believe that this demonstrates that we are achieving, at least in part, our objective of caring better for postoperative surgical patients. Indeed, provision of ITU beds for these patients might represent over-provision.

We are unsure where we 'miss the point' about ITU expansion. Our point is that POCCU or OIR beds are not ITU beds. This allows some flexibility in providing critical care in novel environments. The POCCU allowed the expansion of critical care beds in this Trust. Even if our reduction in cancelled operations was solely due to this expansion, the fact remains that an enlargement of our ITU by four beds could not have been achieved for the same resource as the establishment of the POCCU.

In an ideal world, critical care shortfall would be dealt with by ITU expansion. In ageing hospitals, with scarce resources, we feel it is expedient to provide the best solution we can for our patients.

A. G. Jones
S. J. Harper
Liverpool
UK

1 Jones AG, Harper SJ. Ventilating in recovery—the way forward: Intensive therapy or critical care? *Br J Anaesth* 2002, **88**: 473–4

2 Department of Health. Comprehensive Critical Care. a review of adult critical care services 2000. http://www.doh.gov.uk/pdfs/criticalcare pdf

3 The Intensive Care Society. *Standards for Intensive Care Units*. London: Intensive Care Society, 1997

Anaphylactic reaction to isosulphan blue

Editor—Sentinel lymph node biopsy (SLNB) is a minimally invasive technique, which has been introduced into breast surgery. It has the potential to limit the need for full axillary clearance in patients with positive axillary nodes.[1] The technique uses isosulphan blue dye (Hirsch Industries Inc., Richmond, VA, USA), a patent blue dye derivative, either alone or in combination with a radio colloid, to aid the detection of malignant metastasis to sentinel nodes.[2] We recently treated a 50-yr-old female with breast cancer who developed a severe reaction to isosulphan blue. Anaesthetists should be made aware of the high incidence of adverse reactions to this substance.

The patient was scheduled for left lumpectomy and left axillary SLNB with localization using isosulphan blue dye and technetium-99 sulphur colloid, in an outpatient setting. After radio colloid injection and lymphoscintography, she was transferred to the operating room facility and anaesthesia was induced using fentanyl 150 mg, propofol 120 mg and rocuronium 40 mg. Uneventful anaesthesia continued for 50 min during the initial stages of the operation. After 50 min, the surgeon injected isosulphan blue 3 ml subcutaneously around the tumour. Approximately 30 min after this injection, the patient's systolic arterial pressure fell abruptly from 104 to 70 mm Hg. Over the following few minutes, repeated ephedrine 10 mg and phenylephrine 200 mg boluses were administered intravenously. Her systolic arterial pressure further decreased to 64 mm Hg, and then to 52 mm Hg. Sp_{O_2} declined marginally from 99–100% to 95–96%, as is expected with isosulphan blue. End tidal carbon dioxide concentration remained unchanged. No bronchospasm, rash or urticaria were observed.

Anaesthesia was reduced to the minimum necessary consistent with amnesia, i.v epinephrine 100 µg was given and the patient's arterial pressure increased transiently. Resuscitation continued with i.v. fluids and epinephrine in repeated 100–300 µg i.v. boluses. During the next 30 min, 5–6 litres of i v fluid and epinephrine 2 mg were given. A right radial artery cannula was placed for continuous monitoring of arterial pressure After 30 min, frequent repeated epinephrine boluses were still required to maintain cardiovascular stability. The patient's right internal jugular vein was cannulated, hydrocortisone 100 mg and diphenhydramine 50 mg were administered, and a continuous infusion of epinephrine $400\ \mu g^{-1}\ h^{-1}$ was established Her systolic arterial pressure stabilized at 100–110 mm Hg. Blood was obtained for measurement of serum mast cell tryptase concentration, routine bloods tests, clotting and arterial blood gases. The decision was taken to continue with the lumpectomy to remove excess isosulphan blue and minimize the possibility of a biphasic anaphylactic reaction.[2 3] Concomitant planned gynaecological surgery was cancelled.

After surgery, the patient was admitted to the intensive care unit. She continued to require epinephrine to maintain cardiovascular stability. She also developed orofacial oedema. But after 12 h, the oedema resolved, the epinephrine infusion was weaned and the tracheal tube was removed She was discharged home 3 days after surgery with no residual effects

Sentinel lymph node biopsy has the potential to become a common treatment for patients with breast cancer because it allows effective axillary node clearance without the associated co-morbidity. Isosulphan blue is widely used for SLNB and anaphylaxis precipitated by its use is sufficiently common to be of clinical concern. The manufacturer of the dye suggests a 1.5% incidence of adverse reactions, all of them allergic.[4] The literature quotes a range of between 0.6 and 2.5%.[3 5–8] When the SLNB technique is introduced into clinical practice, the risks associated with isosulphan blue need careful consideration. For instance, perhaps as part of informed consent, patients should be told of the possible occurrence of life threatening complications. We also question whether it is appropriate to administer isosulphan blue in the day case setting—certainly, adequate facilities to care for the patient during and after surgery should be available. Anaesthetic personnel should be aware of these potential problems with isosulphan blue and be equipped to deal with them.

T. B. Stefanutto
W. A. Shapiro
P. M. C. Wright
San Francisco
USA

1 Darzi A, Mackay S Recent advances in minimal access surgery *Br Med J* 2002, **324**. 31–4

2 Krag D, Weaver D, Ashikaga T, *et al* The sentinel node in breast cancer—a multicenter validation study *N Engl J Med* 1998; **339** 941–6

3 Leong SP, Donegan E, Heffernon W, Dean S, Katz JA. Adverse reactions to isosulfan blue during selective sentinel lymph node dissection in melanoma. *Ann Surg Oncol* 2000, **7**: 361–6

4 Hirsh Industries Inc Isosulfan blue 1% aqueous solution (lymphazurin 1%)—product monograph 1983

5 Albo D, Wayne JD, Hunt KK, *et al*. Anaphylactic reactions to isosulfan blue dye during sentinel lymph node biopsy for breast cancer *Am J Surg* 2001; **182**: 393–8

6 Kuerer HM, Wayne JD, Ross MI. Anaphylaxis during breast cancer lymphatic mapping. *Surgery* 2001; **129**: 119–20

7 Cimmino VM, Brown AC, Szocik JF, *et al* Allergic reactions to isosulfan blue during sentinel node biopsy—a common event *Surgery* 2001, **130**: 439–42

8 Longnecker SM, Guzzardo MM, Van Voris LP. Life-threatening anaphylaxis following subcutaneous administration of isosulfan blue 1%. *Clin Pharm* 1985, **4**. 219–21

Shortage of isoproterenol (isoprenaline) hydrochloride

Editor—Since mid-2000, a shortage of raw materials has had a considerable impact on the availability of isoproterenol hydrochloride in the UK and USA. While the US shortage appears to have been resolved in August 2001,[1] commercial supplies of isoproterenol hydrochloride are no longer available in the UK. In May 2002, after exhaustive attempts to locate an alternate source of raw materials of sufficient quality, Forest Laboratories UK Ltd (Pharmax Ltd, Bexley, Kent) reluctantly announced the discontinuation of isoproterenol hydrochloride (*Saventrine IV*™).[2] Celltech Medeva (Leatherhead, Surrey), the only other UK supplier of isoproterenol products, discontinued supplies of *Min-I-Jet® Isoprenaline* in 2001.

While other treatments for symptomatic bradycardia and refractory torsade de pointes do exist, the loss of isoproterenol hydrochloride could potentially pose a serious problem for those involved in cardiothoracic transplantation and cardiac electrophysiology. Fortunately, the sulphate salt of isoproterenol is available from a number of 'special' manufacturers including the Pharmaceutical Manufacturing Unit attached to Torbay Hospital. Isoproterenol sulphate is less potent than the hydrochloride salt and is currently unlicensed in the UK.[3] Isoproterenol sulphate 0.1125% (2.25 mg/2 ml, equivalent to 2 mg/2 ml isoprenaline HCl) should now be available to hospital pharmacies.[3]

J. E. Arrowsmith
Cambridge
UK

1 US Food and Drug Administration, Center for Drug Evaluation and Research web site (http://www.fda.gov/cder/drug/shortages/)

2 Personal communication Caroline Bolton, Medical Information Department, Forest Laboratories UK Ltd, Bexley, Kent DA5 1NX, UK

3 Personal communication· Phil Bendell, NHS Pharmaceutical Manufacturing Unit, Torbay Hospital, UK

The confidential enquiries into maternal deaths in the UK (CEMD)—a 'sub-standard' report?

Editor—I fully subscribe to the widely accepted view that the latest Confidential Enquiries into Maternal Deaths in the UK[1] (CEMD) is the best audit of its kind in the world today, containing marked improvements on the previous one. The title of this letter is only intended to provoke discussion and debate!

The fact that the CEMDs have helped significantly to reduce maternal mortality and morbidity is undoubted, and the recent success story regarding thromboembolism deserves congratulation. However, the fact that the authors have such power to improve practice and change outcomes brings with it a responsibility, for it is incumbent on them to determine where further improvements could be made and to act on them without delay. I believe there could have been a similar success story with regard to hypertension (the second commonest cause of death), if the previous triennial reports had been more specific. Each trimester, I have looked forward to reports of improvement in this respect, but once again the 1997–99 report was disappointing, especially with regard to reporting anaesthetic details and recommendations regarding magnesium therapy.

In contrast, the chapter on haemorrhage was exemplary, with relevant details including the exact stage at which junior and consultant anaesthetists became involved. The recommendation that anaesthetists be involved at an early stage in planning patient management; and that for a woman at known risk of haemorrhage, 'any anaesthetic should be given by a consultant', is strongly worded and unambiguous. I cannot understand why this recommendation has not been extended to other high-risk situations, especially hypertension, HELLP syndrome and sepsis.

The chapter on anaesthesia stressed that delayed or inadequate consultation with anaesthetic colleagues contributed significantly to substandard care, and deplored the fact that anaesthetists are still not considered an important part of the multidisciplinary team. The need to 'be aware of the vital contribution that can be made by anaesthetists when adequate warning is given, and harm that can result when it is not', was emphasized. Sadly, consultant involvement was specified only in two of the 17 cases discussed in this chapter, leaving one to surmise that the vast majority of patients were attended to by trainees alone. It would certainly have been of value to know the level of expertise of the trainees involved (e.g. third year registrar, first year trainee, locum, etc.).

The three deaths directly attributable to anaesthesia also need further comment. In the first instance, when epidural anaesthesia was complicated by a dural tap and converted to a high subarachnoid block for Caesarean section, should not a senior colleague have been called in early so that the first anaesthetist need not have left a healthy young mother to deteriorate, to attend to a dying baby? Should not a consultant have been involved in the second case where a badly planned fifth anaesthetic was given for a scheduled operation on a high-risk mother in intensive care? Although the third death was blamed on over-transfusion with colloids, could it not have been due to acid aspiration?

My strongest criticism of the chapter on hypertension is that the anaesthetic care has been omitted. Most of these patients had very high arterial pressure and died after Caesarean section. Yet the anaesthesia given and the experience of the anaesthetist involved have not been recorded. Perhaps it is not unfair to assume that most of them were done under general anaesthesia by inexperienced juniors who did not use prophylactic measures to obtund the catecholamine surges at intubation and extubation, and the other stressful manoeuvres, which would certainly have contributed to, if not directly caused, intracranial haemorrhage and pulmonary oedema, the causes of death.

The greatest disappointment was that even in this latest report, the place of magnesium has been underplayed. In several instances, various cocktails have been given and magnesium avoided or only resorted to 'too late'. Practising in a developing country, I cannot come to terms with the fact that the simple, tried and tested magnesium therapy is withheld. The recommendations given for the management of pre-eclampsia are far behind the times, magnesium being advocated 'too late', only after seizures have occurred. Magnesium therapy has been standard practice in the USA, Australia and other countries for decades, and its safety and efficacy are well documented. I recall that the UK lagged far behind other countries in changing from magnesium trisilicate to sodium citrate. Are they not making the same mistake with regard to magnesium sulphate?

May I make the following suggestions?

(i) The chapter on hypertension should be reviewed case by case by a multidisciplinary special interest team including practising consultant obstetric anaesthetists.
(ii) The recommendations for pre-eclampsia should be reviewed with a view to early institution of magnesium as a first-line therapy for the prevention of complications and suppression of catecholamine surges, especially during labour and general anaesthesia.
(iii) Recommendations regarding the choice of anaesthetic technique for patients with pre-eclampsia and HELLP syndrome should also mention consultant involvement.

May I also draw attention to the fact that a few typing errors have crept in, such as 20001 for 2001[1]

I hope these points are taken in the spirit in which they are written, hopeful that recommendations may be given before the golden jubilee of the CEMD, so that more young women need not die due to 'sub-standard' care.

N. Rodrigo
Colombo
Sri Lanka

1 *Why Mothers Die. Report on Confidential Enquiries into Maternal Deaths in the United Kingdom 1997–1999.* London: RCOG Press, 2001

British Journal of Anaesthesia 89 (3). 530–3 (2002)

Book Reviews

Problems in Anesthesia Series. L. A. Fleisher and D. S. Prough (editors-in-chief). *Traumacare* R. P. Dutton (guest editor) Published by Lippincott, Williams and Wilkins, Philadelphia. Pp. 423, indexed; illustrated

This book is part of the continuing *Problems in Anesthesia* series published quarterly by Lippincott, Williams and Wilkins. The text is detailed and scholarly and is divided into 12 sections, which cover most of the interface the practising anaesthesiologist has with the increasingly important field of trauma care.

The information is presented in classic American monograph style and is generally readable, although the font size in some of the reduced diagrams had this reviewer reaching for his number two spectacles Doubtless, younger eyes will fare better but may desire more use of the text box in future volumes of the series to present key synopses, particularly since there are no detailed summaries of chapter contents.

The contributors are leading experts in the field and are almost all from the United States. Although authoritative, this selection gives only a partial view of the involvement of anaesthetists in trauma care worldwide, particularly in Europe where they are routinely involved in prehospital emergency care The role of anaesthetists in this text is confined to involvement with the progression of the patient through hospital. Field and disaster anaesthesia are not considered.

The guest editor and many of the contributors come from the Baltimore Shock Trauma Center, which has done so much to further advancement in this field. The text is presented in a multidisciplinary way, but there is a logical progression of the management of the trauma patient from the emergency room right through to the intensive care unit.

Trauma is now the main cause of death in certain parts of the world, particularly in the younger age groups, and the best management is gained by the trauma team approach. The key role of the anaesthetist in this team is emphasized from the outset and there is a major central chapter given over to the prioritizing of surgery for the trauma patient. Here the anaesthetist plays an essential role as the 'gatekeeper' of the operating theatre, and has a large responsibility for ensuring correct resuscitation measures have been taken and that surgery for life-threatening injuries is conducted first.

The early chapters of the text concern the assessment and early management of the trauma patient and follow essentially the well-established protocols set out by the ATLS course developed by the American College of Surgeons. Despite the relative clinical rigidity of this approach, there is sensible council about the need for dynamic and integrated assessment and resuscitation, and advice on when it is necessary to break the rules of the ATLS system

Airway and ventilation management are rather loosely entwined in the text and greater emphasis could have been given to the need for effective ventilation as an immediate reflex following establishment of the airway Techniques of IPPV are given only cursory treatment and confined to the use of the bag valve mask. The valuable role of the portable automatic ventilator is absent, possibly because it has been more widely used in emergency medicine in countries other than the United States.

Airway management is rightly given detailed treatment with good discussion of devices such as the LMA[†] and Combitube. Curiously, the essential technique of cricothyroidotomy is relegated to the practice of the emergency physician, but should be firmly within the capabilities of the trauma anaesthetist. Cervical spine management is given careful treatment in the airway section

There follows a good overview of the theoretical and practical aspects of the management of traumatic shock, with a clinical discussion covering early and late resuscitation and the importance of treatment before irreversibility sets in. A section on fluid replacement follows a discussion of the pathogenesis of traumatic shock, and moves the debate beyond the usual impasse of crystalloid *vs* colloid, emphasizing the key goal of oxygen delivery.

The central pivotal chapter on the role of the anaesthetist in overall management provides a logical approach to the management of the airway, control of haemorrhage, traumatic brain injury, the realities of thoracic trauma, and finally, limb-threatening injury and time-dependent systemic infection. This chapter will be a valuable tool for the anaesthetist involved in the overall management of surgical priorities. They take serious decisions on who must make risk–benefit analyses for each case, allowing for potential complications from a delay in surgery.

The remainder of the book is given over to a clear account of the management of closed head injuries and a collection of chapters devoted to the pathophysiology of trauma, spinal cord injury, trauma in the young, pain, and burns management. There is a very useful chapter on the management of post-traumatic respiratory failure and an analysis of the management of ARDS in the light of the findings of the 2000 consensus conference held in Barcelona.

This monograph should find a very useful place as a source reference for all anaesthetists involved in trauma for many years to come The editors and publisher are to be congratulated in producing a definitive text at a very affordable price. Although certain sections, particularly the chapter on mediators of tissue injury, may appear rather indigestible, repeated reading will reveal a rich source of useful information for those anaesthetists who will be increasingly involved in the front line management of trauma.

D. J. Baker
Paris
France

Accident and Emergency Diagnosis and Management. 4th Edn Anthony F. T. Brown Published by Arnold, London. Pp. 442; indexed; illustrated. Price £18 99 ISBN 0340807202.

This pocket-sized handbook is aimed at senior house officers in emergency medicine. The author promises 'practical didactic advice' on managing 'every patient, however unusual, complex or unexpected the presentation'. By and large, he delivers on this promise.

The book is comprehensive and concise. Basic medical and surgical emergencies are adequately covered. Critical points in consolidating a diagnosis are followed by a clear outline of management priorities for all common emergency conditions. The section on administrative and legal considerations is excellent. It covers dealing with the police, consent to treatment, and many other difficult issues All junior doctors should read this chapter before starting work in an Accident and Emergency (A&E) department. It would go a long way towards keeping them out of trouble The book is well indexed and cross-referenced. Web-based resources are included, as are contact numbers for relevant organizations, such as the UK National Poisons Centre.

[†] LMA® is the property of Intavent Limited

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

The title 'Diseases imported from abroad' for the tropical medicine section irked me somewhat. Abroad is a relative term. The inclusion of HIV infection in this section would seem bizarre to those of us based in British cities. The HIV infection we see is locally acquired rather than imported! The chapter hardly mentions tuberculosis, which is becoming ever more important. The section on neck sprains is, similarly, too short. X-rays are advised for all patients, although evidence-based guidelines exist which identify patients who do not necessarily need an x-ray.

It must be difficult with a core handbook such as this, to compromise between the constraints of being pocket-sized and being comprehensive. I did not find the format attractive. The text is dense and key information seems hidden in the middle of pages. More diagrams and algorithms would give the presentation a more contemporary feel. The crucial points would be more obvious. Most junior doctors would value some spaces to include scribbles, so as to cross reference the book's recommendations with local practice.

There will inevitably be areas of conflict between a core handbook, such as this, and locally developed guidelines. I identified numerous differences with my departmental guidelines, mainly in drug therapies. There is always a problem keeping a published text up-to-date and the anti-tetanus policy has already been changed in the UK to include diphtheria immunization. Locally developed departmental guidelines may lessen the need for a handbook such as this.

I expect that most young UK consultants relied on previous editions of this book, or similar texts, to keep them on the right track when they were senior house officers for the first time in A&E. Nowadays, in most teaching hospitals, junior doctors are better supported. I was disappointed, therefore, that the importance of calling early for senior support was not emphasized enough in this book. Thankfully, modern emergency care is based on experienced emergency physicians, not junior doctors working from handbooks.

This book is a good core handbook of emergency care. Junior doctors will find it reassuring to have a copy of this book in their pockets when starting those first long night shifts in the emergency department They will not go far wrong with this book, once they remember to call for help too.

U. Geary
Liverpool
UK

Handbook of Obstetric Anaesthesia. C. M. Palmer, R. d'Angelo and M. J. Paech. Published by BIOS Scientific Publishers Ltd, Oxford Pp. 266; indexed; illustrated. Price £60.00. ISBN 1-85996-232-7.

This book is designed as a guide to practical obstetric anaesthesia and aims to be a quick reference for trainees and consultant anaesthetists working in this area. The contents section shows clearly the chapters together with their relevant subsections, and this simplifies matters for the anaesthetist seeking help on a particular topic. The content is easily readable and there are a plethora of tables, charts and diagrams in each section which summarize the accompanying text. This makes for quick, easy reference. The sections are nicely balanced and cover essentially all areas of relevance to the obstetric anaesthetist. At 260 pages, it is easy to read through and use to revise concepts before examinations.

There is a good introductory section that summarizes the development of obstetric anaesthesia. Thereafter, there are excellent chapters on obstetric physiology, neonatal physiology, and neuroanatomy and neuropharmacology which anyone revising for examinations would find invaluable. The chapter on antenatal monitoring fails to mention fetal blood vessel ultrasonography and fetal scalp electrodes.

Chapters 5–8 present anaesthesia for vaginal delivery, anaesthesia for Caesarean section, and methods of postoperative analgesia. These chapters are less succinct but the subjects are difficult to summarize. In this area, the book does not offer much advantage over other books already in circulation Also in this section, much of the discussion is relevant to US practice and not especially to UK practice.

The chapters on pregnancy-induced hypertension and coexisting disease are excellent, as is the section on complications of obstetric anaesthesia and analgesia, which has a useful summary of postpartum nerve dysfunction. A chapter on obesity is particularly welcome. The sections on neonatal resuscitation and medicolegal considerations are well worthwhile.

This book largely succeeds as an easy reference guide for obstetric anaesthetists, but at £60.00 it is probably too expensive for the trainee to buy. It is also mainly aimed at the North American market, and has almost exclusively North American references. Not all sections translate well into British practice However, it is a useful reference book to have in the department for trainees to revise from and refer to. I can recommend it for this purpose.

B. Loughnan
Harrow
UK

Critical Care Focus. Number 8: *Blood and Blood Transfusion*. Helen F Galley Published by BMJ Books, London. Pp 85, indexed; illustrated. Price £14.95. ISBN 0727916572.

This is another in a series of short books produced in association with the Intensive Care Society. These are not comprehensive textbooks, but comprise concise chapters on specific topics relevant to the critically ill. The seven chapters in this volume cover the function of blood and administration of blood products in the critically ill.

Two chapters describe recent large, influential studies in intensive care and will be of considerable interest to the practising intensivist. Martin Tweeddale gives a balanced description of the Transfusion Requirements in Critical Care study, that showed that restrictive transfusion practice was associated with similar mortality to liberal use of red cells. The results of this study are widely known and its recommendations have been adopted by many intensive care units. What I liked about the chapter was the description of the background and lead-up to the study, the detail about study design, and the hints of what actually happened during the study itself, particularly in relation to exclusions. These are less apparent from the formal publications. Pierre-Francois Laterre contributes a similarly balanced description of the PROWESS study, which showed reduction in mortality in patients with severe sepsis treated with human recombinant activated protein C. The background information is a concise description of the confusing area of inflammation–coagulation interaction during sepsis, which clinicians will find helpful. The discussion of the problems of translating study findings to the wider ICU population, particularly with reference to bleeding risk, was also good.

The other chapters cover a mixture of topics. Machin gives a nice overview of haemostatic problems in the ICU, with particular reference to platelet function. There is plenty of practical advice and I thought the section on heparin-induced thrombocytopenia was a useful summary of a subject that causes considerable confusion. The chapter on Transfusion Associated Lung Injury (TRALI) is a well-written account of a poorly understood condition that is probably often missed. The authors make comparisons with recent advances in the understanding of

ARDS pathophysiology, which may stimulate thought amongst those interested in this subject. The section describing how to investigate a possible case of TRALI is particularly useful.

Cooper's chapter called 'Radical reactions of haem proteins' sounds heavy going, but was a useful insight into the chemist's view of free radical chemistry. It is particularly relevant to those interested in artificial haemoglobin-based oxygen carriers. It discusses the challenge faced in stopping haemoglobin molecules from binding nitric oxide and inducing vasoconstriction, and in avoiding oxidant damage from their tendency to change from ferrous to ferric or ferryl forms I also learnt that substances like mannitol that are supposed to be free radical scavengers cannot fulfil this role *in vivo*; another myth dispelled! The section on rhabdomyolysis argued elegantly that alkali does not increase myoglobin solubility in urine, but does decrease renal damage by reducing free radical haem damage.

The two other chapters, on colloids and leucodepletion of blood products, were a little disappointing. The former gave a nice historical overview and discussed the problems of carrying out outcome studies in this area, but I thought the literature review was rather selective. Nielson's chapter on bioactive substances in blood and the importance of leucodepletion was dominated by the author's own data. The literature review was very selective, did not include important meta-analyses, and did not mention recent changes to blood processing practices (leucodepletion at source), in the UK and many other countries. In my opinion, the messages from this chapter were confused and potentially misleading to those unfamiliar with the area.

In summary, this book is exactly what it claims to be—a mixture of current opinion. It is an easy, inexpensive account of some issues around the blood and critical illness. I think it is best suited to the more experienced clinician rather than trainees in anaesthesia or intensive care, and some chapters should interest haematologists and transfusion medicine specialists who want to keep up-to-date with ICU issues.

T S. Walsh
Edinburgh
UK

Cardiac Arrhythmias. Practical Notes on Interpretation and Treatment. 6th Edn. David H. Bennett. Published by Arnold, Hodder Headline Group, London. Pp. 340; indexed, illustrated. Price £29 99. ISBN 0340807318.

This book comprises 27 chapters. The first 18 chapters describe the interpretation and treatment of the main rhythm disturbances of the heart, including four chapters on AV block, sick sinus syndrome, syncope, and arrhythmias due to myocardial infarction. The next eight chapters cover treatment. anti-arrhythmic drugs, cardioversion, cardiac pacing, catheter ablation, and cardiopulmonary resuscitation There is also a chapter on ambulatory monitoring The final chapter is a quiz and gives a number of ECGs for interpretation.

In the preface to the first edition, it states that this book is intended to fill the gap between those books that cover basic arrhythmias and books intended for electrophysiologists This edition achieves its aim It is a book written to be understandable by readers who have little knowledge of the electrocardiographic features of the main cardiac arrhythmias. The salient features of the main arrhythmias are simply described and illustrated in the numerous electrocardiograms that accompany the text, the available treatments and approaches to prevention are discussed, and the main points are summarized at the end of each chapter.

The chapters are brief and very readable; unfortunately, the necessary corollary of this is that the mechanistic explanations are sometimes either cursory or non-existent. In the introduction, the author alludes to the importance of examining multiple simultaneously recorded ECG leads. But, unfortunately, many examples are illustrated in a single lead only. Similarly, for many of the ECGs given in the quiz section, the lead is not labelled. There is a typographical error on page 52; atrial rate should be ventricular rate The final chapter is a strong point of the book. Not being able to interpret a quiz ECG should motivate the reader to read the appropriate chapter. ECGs are rarely interpreted in isolation and a short, single sentence of history could have been provided to accompany most of the practice ECGs.

Most of the intended purchasers of this book are unlikely to read the *British Journal of Anaesthesia.* The important question then is how relevant is this book to an anaesthetic readership? I enjoyed reading it and would recommend it unreservedly to anaesthetists who wish to improve their knowledge of cardiac arrhythmias. My advice is to buy the book and read it.

S. H. Pennefather
Liverpool
UK

Anaesthesia OSCE. 2nd Edn G. Arthurs, K. M. Elfituri. Published by Greenwich Medical Media, London. Pp. 453; illustrated. Price £24.50. ISBN 1841100870.

Anaesthesia OSCE has been written as an aid for candidates preparing for the Primary FRCA examination. The second edition of this book has been extensively revised with the addition of new material. In OSCEs, candidates are required to apply their knowledge to answer questions clearly and concisely. This book enables them to practice answering realistic OSCE questions. It encourages them to do so with constructive and supportive feedback from their senior colleagues. The format of this book is well laid out; the questions are followed by a detailed tutorial on that subject. On the whole, it is well presented, concise, and full of useful information.

The introduction provides a brief but worthwhile discussion of the necessary preparation for OSCEs, with emphasis on frequent practice, and orderly presentation. The book is divided into 14 chapters, covering various stations encountered in the examination. The chapters on 'History Taking' and 'Physical Examination' give a quick, structured and systematic approach to the patient with several examples (e.g taking history from a patient with thyroid disease, examining the cardiovascular system, examining cranial nerves, etc.). The introduction in the chapter on communication skills was excellent, but some of the communication scenarios are rather verbose. Questions 9–16 in this section will certainly give a new perspective not only to the trainee/candidate, but also to the OSCE steering group at The Royal College of Anaesthetists. For instance, one question involves explaining to a trainee anaesthetic technician about application of cricoid pressure in rapid sequence induction, and another requires the candidate to explain to a patient why their tooth was knocked out accidentally during intubation.

The resuscitation chapter is well presented according to the Resuscitation Council Guidelines, with algorithms for Basic Life Support and Advanced Life Support In the anaesthetic equipment chapter, question number seven on the anaesthetic machine was a little ambiguous The line diagram of the anaesthetic machine was difficult to follow In reality, some of the questions in this chapter and in the one on monitoring equipment were too extensive for one OSCE station. In the first OSCE in the monitoring equipment chapter, there was also some disparity. There were five questions but six answers.

In the measuring equipment chapter, the questions on direct arterial pressure monitoring, spirometer loops, temperature measurement, and humidity were well presented. Regarding the question on peripheral nerve stimulators, no doubt all those groups of muscle mentioned will contract, but the main muscle that we monitor and record from is the adductor pollicis. This point should be emphasized in the answer. The introduction to the chapter on anaesthetic hazards was excellent, with clear information on minor points, which often cause confusion (e.g. the meaning of inductor, capacitor, electrical filter; etc.). In the chapter on 'Skill', some of the questions are vague, and not well structured. Incontrast, all the questions in the chapter on anatomy are at an appropriate standard for the primary examination. The chapter on statistics has an excellent introduction on various statistical tests, but has only two questions in it, which are in multiple-choice format. This is probably not appropriate for an OSCE. The chapters on x-ray, ECG and data interpretation are well laid out, but the question on the echocardiogram may be too detailed for the Primary FRCA examination.

In summary, however, this is a useful book for those preparing for the Primary FRCA examination. I would recommend it to them.

B V S Murthy
Liverpool
UK

Guide to Contributors

The purpose of the *British Journal of Anaesthesia* is the publication of original work in all branches of anaesthesia, including the application of basic sciences. One issue each year deals mainly with material of postgraduate educational value.

Papers for publication and all editorial communications should be addressed to: Professor J. M. Hunter, Editor-in-Chief, *British Journal of Anaesthesia*, University Department of Anaesthesia, Royal Liverpool University Hospital, The Duncan Building, Daulby Street, Liverpool L69 3GA, UK. Tel./Fax: +44 (0) 151 706 4005. E-mail: bja@liv.ac.uk

Papers

Papers submitted must not have been published in whole or in part in any other journal, and are subject to editorial revision. It is a condition of acceptance for publication that copyright becomes vested in the journal and permission to republish must be obtained from the publisher.

Papers based on clinical investigation should conform to ethical standards as set out in the Declaration of Helsinki and should normally include a statement of approval from an appropriate Ethics Committee. In the case of animal studies it is the responsibility of the author to satisfy the Board that no unnecessary suffering has been inflicted. Studies from the UK should specify the Home Office Licence number; from elsewhere, a statement of approval from an appropriate licensing authority.

Legal considerations

Authors should avoid the use of names, initials and hospital numbers which might lead to recognition of a patient. A patient must not be recognizable in photographs unless written consent of the subject has been obtained. A table or illustration that has been published elsewhere should be accompanied by a statement that permission for reproduction has been obtained from the authors and publishers.

Preparation of manuscript

Four copies of each manuscript (including revised texts) should be submitted and should indicate the title of the paper, the name(s), full address(es) of the author(s), and be in letter quality heavy type (not dot matrix), double-spaced on one side only of the paper, with a wide margin. Contributors should retain a copy in order to check proofs and in case of loss. Where possible, manuscripts should also be submitted on disk. Our preferred format is a 3.5″ PC floppy disk with the file written in Word 6 for Windows. However, it is also possible to process disks submitted in other formats, provided sufficient information is supplied to enable conversion to the preferred format. Articles on disk should be prepared in the simplest possible form. Please do not use endnotes, footnotes, etc. for references. Correct fonts, type sizes, column measures, etc, will be added by the technical editor.

Each of the four copies submitted must be accompanied by a complete set of figures. One set of figures must be unmounted glossy prints (see below); the three other sets may be photocopies.

Manuscripts should be accompanied by a formal letter of request for publication which should be signed by all the authors. There should be a clear declaration of any financial or commercial interest which any author may have in the material. The Editor may wish to see raw data if necessary.

Papers in recent issues of *British Journal of Anaesthesia* should be consulted for general and detailed presentation. They are most often subdivided into:

Title page
Summary, including Keywords
Introduction (not headed)
Methods
Results
Discussion
Acknowledgements
List of references
Tables (including legends to tables)
Illustrations (including captions)

Title page

There should be a separate title page, including the name(s) and address(es) of all author(s). It should be made clear which address relates to which author. Authors' present addresses differing from those at which the work was carried out, or special instructions concerning the address for correspondence, should be given and referenced at the appropriate place in the author list by superscript numbers. If the address to which proofs should be sent is not that of the first-mentioned author, clear instructions should be given in a covering note and not on the title page. The title page should be paginated as page 1 of the paper.

A short running title containing not more than 50 characters and spacing should be included.

Summary

The summary will be printed at the beginning of the paper. It should be on a separate sheet, in structured format (Background; Methods; Results; and Conclusions) for all original articles (Clinical Investigations, Laboratory

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Investigations, and Short Communications) but not for Reviews, Case Reports, or Commentaries. It should give a succinct account of the problem, in up to 250 words. It may be used as it stands by abstracting journals. References are not used in this section, except in exceptional circumstances.

Three to five key words or phrases (for indexing) should be included below the summary.

Introduction

The introduction should give a concise account of the background of the problem and the object of the investigation. Previous work should be quoted only if it has a direct bearing on the present problem.

Methods

Methods must be described in sufficient detail to allow the investigation to be interpreted and repeated by the reader. Any modification of previously published methods should be described and the reference given. If the methods are commonly used, only a reference to the original source is required.

Drugs

When a drug is first mentioned it should be given the international non-proprietary name, followed in parentheses by the chemical formula only if the structure is not well known, and by the capitalized proprietary name.

Results

Description of results, while concise, should permit repetition of the investigation by others. Data should not be repeated unnecessarily in text, tables and figures, and unwarranted numbers of digits should be avoided. Significance should be given as values of probability.

Discussion

The discussion should not merely recapitulate the results, but should present their interpretation against the background of existing knowledge. It should include a statement of any assumptions on which conclusions are based.

Acknowledgements

Acknowledgements will be printed in small type. They should be brief, and should include reference to sources of support and sources of drugs not freely available commercially. Individuals named must be given the opportunity to read the paper and approve their inclusion in the acknowledgements, before the paper is submitted.

References

There should be a list of references at the conclusion of the paper, commencing on a new sheet.

References must be numbered consecutively in the order in which they are first mentioned in the text, with the exception of review articles, when references should be arranged alphabetically.

References in text, tables and legend should be identified by arabic numbers appearing in the text in superscript, for example ^{5} or $^{5-7}$ or $^{5\ 16}$ for unrelated references. When a table or figure is first mentioned, its reference must continue the sequence.

Use the style of references adopted by the US National Library of Medicine and used in *Index Medicus.* The titles of journals should be abbreviated.

The names and initials of more than six authors should be abbreviated to three authors followed by *et al.*

Text references to 'unpublished observations' or 'personal communications' should not be included in the final list of references. Authors are responsible for verifying that the wording of references to unpublished work is approved by the persons concerned. Papers which have been submitted and accepted for publication should be included in the list, the phrase 'in press' replacing volume and page number. Information from manuscripts submitted but not yet accepted should be cited in the text as unpublished observations.

Examples of correct forms of references:

Journals:

1. Brown BR jr, Gandolphi AJ Adverse effects of volatile anaesthetics *Br J Anaesth* 1987; 59: 14-23

Chapter in a book:

2. Hull CJ Opioid infusions for the management of postoperative pain In Smith G, Covino BG, eds. *Acute Pain.* London Butterworths, 1985; 155-79

Monographs:

3. Moore, DC. *Regional Block*, 4th Edn. Springfield, Illinois: Charles C Thomas, 1979

Restrict references to those that have direct bearing on the work described and cite only references to books and articles published in *Index Medicus* journals.

It is essential that authors verify the content and detail of references which they list against the original articles, as this responsibility cannot be accepted by either Editors or publishers.

Tables

All tables should be on separate sheets and be capable, with their captions, of interpretation without reference to the text. They should be numbered consecutively with Arabic numerals. Units in which results are expressed should be given in brackets at the top of each column, and not repeated on each line of the table. Ditto signs are not used. Footnotes are not used.

Illustrations

Photographs should be unmounted glossy prints, and should be protected adequately for mailing. Surfaces should not

be marred with clips, pins or by heavy writing on the back. Drawings, charts and graphs should be in black indict ink on white paper and, if in sets, should be presented at a uniform magnification. Illustrations should be clearly numbered on the back, preferably in soft pencil, with reference to the text, and using Arabic numbers. They should be accompanied on a separate sheet by a suitable legend. Lettering should be professional-looking, uniform, preferably in a common typeface, large enough to read at a reduced size, and in proportion to the illustrated material. Lines in the original must also be thick enough to allow for reduction. Magnifications, especially in photomicrographs, should be indicated by a scale on the photograph itself, in order to remain appropriate after reduction. Symbols which are to appear in the figure (and not in the legend) should be chosen from the following available types:

● ○ ■ □ ▼ ▽ ▲ △ ◆ ◇ × +

The names of the author and title of the paper should also be written in soft pencil on the back of the illustrations.

It should be noted that A4-size figures generated by computer are usually unacceptable (see Extended Guide to Contributors—*Br J Anaesth* 2000; **84**: 131-7).

General information

Instructions to the printer. Words to be printed in lowercase italics should be indicated by one underline. Two underlines indicate small capitals, three indicate large capitals and four, italic capitals. A wavy underline indicates a word to be printed in bold type.

Headings in the text. Three possible grades are available, and may be indicated by the following letters of identification.

A **Results (bold)**
B *Lung function studies* (italics, ranged left)
C *Volume.* Large volumes... (italics, ranged left, text run on)

Symbols and abbreviations. In accordance with Editorial adoption of SI units, abbreviations and symbols should follow the conventions described in the booklet *Units, Symbols and Abbreviations. A Guide for Biological and Medical Editors and Authors* (D. N. Baron, ed.) (1988), published by and available from The Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE. Words for which abbreviations are not included should be written in full at first mention in the summary and again in the text and followed by the abbreviation in brackets. This will usually be in the form of large capitals without separating points.

Spelling, etc. British spelling should be used with 'z' rather than 's' spelling in, e.g. organize, organization.

Short communications

Authors are encouraged to submit short manuscripts suitable for rapid publication. In general, these should conform to the requirements outlined above, but with the following differences:

Format. Summary; Introduction (not headed); Methods and results; Comment.

Size. Not more than 6 references, 1 table or 1 figure, one-and-a-half pages of printed text (1200 words).

Correspondence

Each issue of the journal will contain correspondence. Correspondence arising from papers in a recent issue is published without delay, and for this reason, will be given priority over that pertaining to original research. The Editor may change, delete or modify in any way all items of correspondence.

All communications designed for publication should be submitted on a separate page in letter quality heavy type (not dot matrix), double-spaced, on one side only of the paper, with a wide margin. Contributors should send three copies of all correspondence to the editor and retain a copy in case of loss. Correspondence must also be submitted on disk. All authors must sign the accompanying submission letter. A fax number and an E-mail address should be supplied.

Proofs

These should be corrected and returned to the publisher by post or fax within 48 h of receipt. Overseas contributors may fax a copy of the proofs to the publisher but should return their proofs by air mail also.

Reprints

Corresponding authors will receive a copy of the journal in which their article appears. Offprints can be supplied if application is made on the order form attached to the proofs. The order form should be returned with the proofs.

IMPORTANT NOTICE TO AUTHORS

Electronic submission of new manuscripts to the British Journal of Anaesthesia. Please note that, from January 2003, the Editorial team requests that all new manuscripts (excluding Letters to the Editor and Book Reviews), be submitted electronically to the *British Journal of Anaesthesia* web site at: http://bja.manuscriptcentral.com

Clear instructions for submission of new manuscripts are available on this web site. If these instructions are not adhered to, difficulty will be experienced in submitting new articles. For an interim period, manuscripts may also be submitted as hard copy to the Editor-in-Chief's office. It is envisaged, however, that this arrangement will be discontinued by the end of 2003.

ANESTHESIA & ANALGESIA

Journal of the International Anesthesia Research Society, the Society of Cardiovascular Anesthesiologists, the Society for Pediatric Anesthesia, the Society for Ambulatory Anesthesia, the International Society for Anaesthetic Pharmacology, and the Society for Technology in Anesthesia

EDITORIAL

263 Rescue Is Stressful

CARDIOVASCULAR ANESTHESIA (Society of Cardiovascular Anesthesiologists)

266 Arterial Pressure, Jugular Venous Saturation, Insulin, and CPB
273 Tachycardia, Hypertension, and Outcome
278 Splanchnic Oxygenation and Serum Hyaluronate
287 Aprotinin and Major Orthopedic Surgery
294 Lactated Ringer's Solution for Large Volume Infusion
299 Pulmonary Trunk Rupture and Continuous Cardiac Output PA Catheter (Case Report)
302 Pulmonary Artery Catheter Malfunction (Case Report)
305 Cannulation of a Persistent Left Subclavian Vein (Case Report)
308 Retrieval of Entrapped Guidewire (Case Report)
310 Bidirectional Tachycardia (Case Report)
316 Persistent Tachycardia and Dexmedetomidine (Case Report)
319 Accelerated Idioventricular Rhythm and Desflurane (Case Report)
322 False BIS with Forced Air Flow (Case Report)
324 Autotransfusion Device to Prevent Hyperkalemia (Case Report)

PEDIATRIC ANESTHESIA (Society for Pediatric Anesthesia)

326 Thoracic Epidural Placement via Caudal Approach
331 Unexpected Tracheomalacia and Marfan Syndrome (Case Report)
333 Esophageal Atresia and Esophageal Bronchial Reimplantation (Case Report)
336 Pediatric Anesthesia for Voluntary Services Abroad (Review Article)

AMBULATORY ANESTHESIA (Society for Ambulatory Anesthesia)

351 Distal Nerve Blocks for Carpal Tunnel Surgery

ANESTHETIC PHARMACOLOGY (International Society for Anaesthetic Pharmacology)

356 Anesthetic Interactions with the Acetylcholine Receptor
362 Ach Receptors, Volatile Anesthetics, and Muscle Relaxants
368 Perfluorocarbons, Blood Solubility, and Volatile Anesthetics
373 Midazolam-Induced c-Fos and EGR-1 Expression
379 Mivacurium and Hypertension
385 Blue Dye Reactions in Sentinel Lymph Node Mapping
389 Atropine's Effects During Propofol Anesthesia
393 Tizanidine Reduces MAC
397 Fluoride and Mivacurium Metabolism (Brief Report)
400 Verapamil and Electroconvulsive Therapy (Brief Report)

PAIN MEDICINE

403 Epidural Steroid Injection Survey
409 Managing Ergot-Induced Gangrene (Case Report)

ECONOMICS, EDUCATION, AND HEALTH SYSTEMS RESEARCH

411 Learning Curves

CRITICAL CARE AND TRAUMA

417 Midazolam and Stress During Emergency Medical Service

NEUROSURGICAL ANESTHESIA

423 Mechanisms of Intracranial Pressure Modulation by Epidural Blood
430 Propofol and Craniotomy

OBSTETRIC ANESTHESIA

436 Intraspinal Morphine in Cesarean Delivery
441 Intrathecal Analgesia, Lumboperitoneal Shunt, and Enoxaparin (Case Report)

REGIONAL ANESTHESIA

444 Epidural Ropivacaine with Morphine
450 Postoperative Pain Relief After Laparoscopic Cholecystectomy
457 Intravenous Regional Anesthesia: Ketorolac
461 Intraoperative Sedation with Dexmedetomidine
467 Temperature Control During Laparoscopic Surgery
472 Thoracic Epidural Analgesia Survey (Special Article)

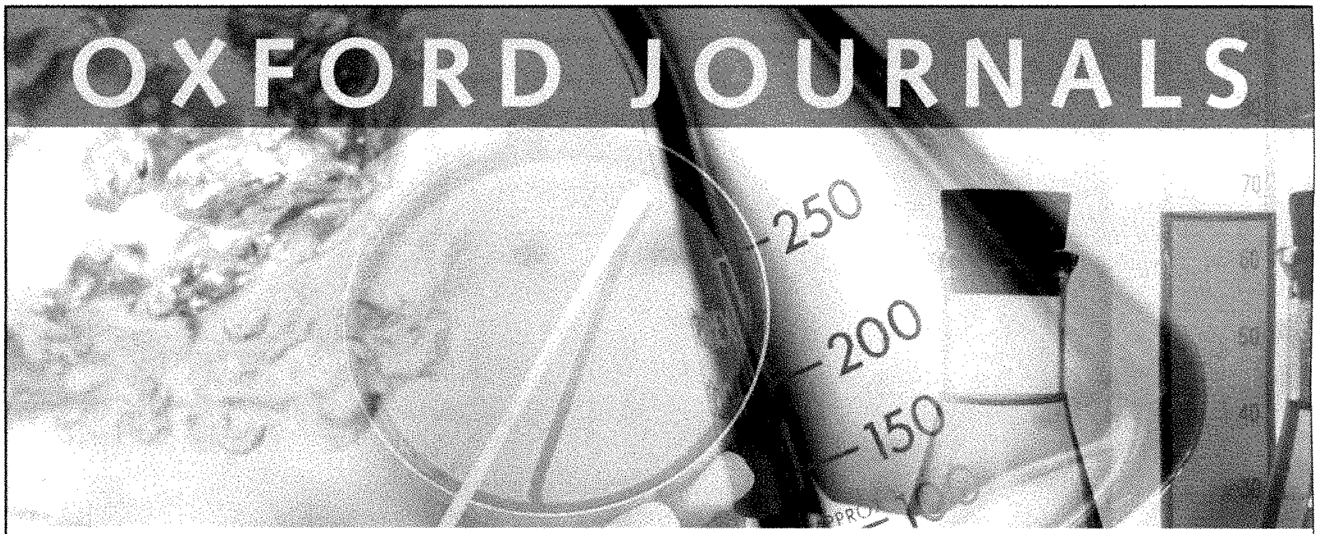
GENERAL ARTICLES

476 Gastric Emptying Is Not a Predictor of PONV
480 Tracheal Intubation with Trachlight®
485 Respiratory Arrest After Laser Treatment (Case Report)
487 Treatment of Accidental Intraarterial Injections (Case Report)
492 One-Lung Anesthesia in Tracheal Bronchus (Case Report)
494 Anesthesia as Therapy for Persistent Hiccups (Case Report)
496 LETTERS TO THE EDITOR
505 BOOK AND MULTIMEDIA REVIEWS

STA PRECONVENTION ISSUE

SEE INFORMATION INSIDE

ISSN 0003-2999 Volume 95, Number 2, August 2002
www.anesthesia-analgesia.org



Medicine

www.oupjournals.org/medicine/?f2

Oxford University Press publishes some of the most respected and highly-cited medical journals in the world including:

BJA: British Journal of Anaesthesia

Human Reproduction

Journal of Antimicrobial Chemotherapy

Nephrology Dialysis Transplantation

Rheumatology

➲ FULL TEXT *now online*

If you are a current print subscriber (institutional or personal), visit **www3.oup.co.uk/Register/?f2** to activate your online access.

➲ FREE @ the web site:

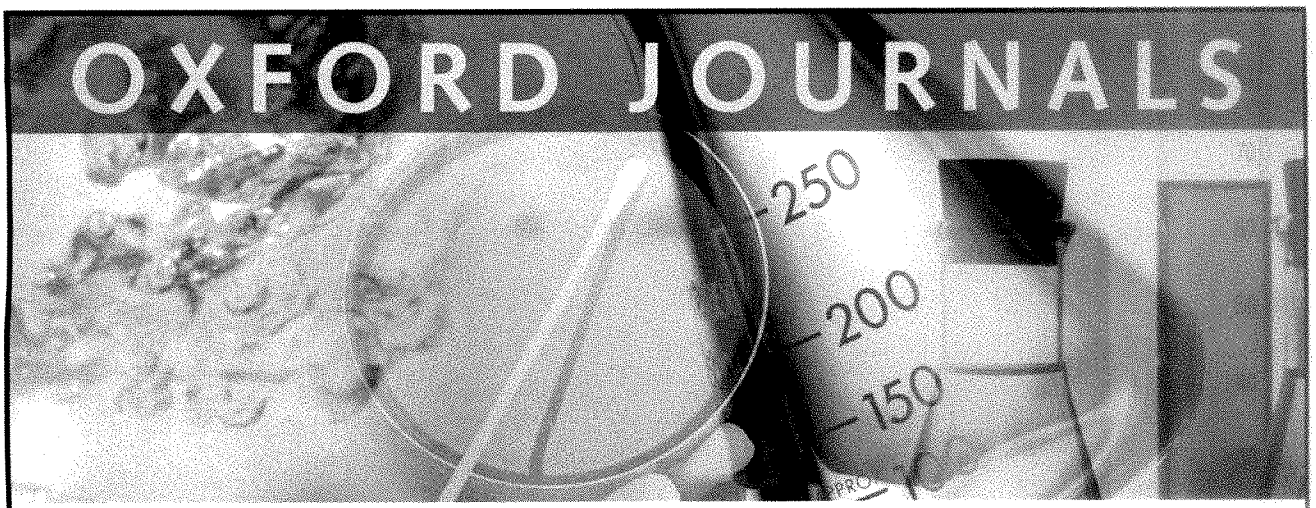
- **tables of contents by e-mail**
- **sample issues**
- **abstracts and tables of contents**
- **instructions to authors**

To subscribe to the above journals, visit the web site @
www.oupjournals.org/medicine/?f2

For further information please contact:
Journals Dept. • E-mail: jnls.cust.serv@oup.co.uk
Tel: +44 1865 267907 • Fax: +44 1865 267835

In the Americas, please contact:
Journals Dept. • E-mail: jnlorders@oup-usa.org
Tel: +1 800 852 7323 (USA/Canada) or +1 919 677 0977
(outside USA/Canada) • Fax: +1 919 677 1714

OXFORD
UNIVERSITY PRESS



OXFORD JOURNALS

BJA CEPD Reviews

www.oupjournals.org/list/bjarev/?f2

Editor-in-Chief: David J Rowbotham

BJA CEPD Reviews is a joint venture of the British Journal of Anaesthesia and The Royal College of Anaesthetists in collaboration with the Intensive Care Society and Pain Society.

The purpose of ***BJA CEPD Reviews*** is the publication of material to support the continuous medical education and professional development of specialists in anaesthesia, critical care medicine and pain

To subscribe, visit the web site @
www.oupjournals.org/list/bjarev/?f2

For further information please contact:
Journals Dept. • E-mail: jnls.cust.serv@oup.co.uk
Tel: +44 1865 267907 • Fax: +44 1865 267835

In the Americas, please contact:
Journals Dept. • E-mail: jnlorders@oup-usa.org
Tel: +1 800 852 7323 (USA/Canada) or +1 919 677 0977
(outside USA/Canada) • Fax: +1 919 677 1714

OXFORD
UNIVERSITY PRESS

Anaesthesia Pain Fellowship
McMaster University, Hamilton, Canada

Applications are invited to an Anaesthesia Pain Fellowship at McMaster University. Referrals in Pain Clinics from Central-South and Northwestern regions, Province of Ontario. Annual visits 10,000 - 12,000. Services include acupuncture, nerve blocks, implantable nerve stimulators, etc.

DEADLINE FOR APPLICATIONS:
OCTOBER 30, 2002

Further information is available on the website:
www.fhs.mcmaster.ca/anaesthesia/education
or from:

Mrs. Mary Gahagan, Office of the Chair,
Department of Anaesthesia,
McMaster University, 1200 Main St. W.,
Hamilton, Ontario, Canada L8N 3Z5
Tel: 905-521-2100 Ext. 75166
Fax: 905-523-1224
e-mail: gahaganm@mcmaster.ca

Queen's
UNIVERSITY

12th Annual

WHISTLER WINTER ANESTHESIA
Refresher Course & Review

February 22 – February 28, 2003

Whistler, British Columbia, Canada

22 hours CME credits
Poster presentations

For information:

Whistler Winter Anesthesia Meeting
Department of Anesthesiology
Kingston General Hospital
76 Stuart Street
Kingston, Ontario, Canada, K7L 2V7

Voice Mail: (613) 549-6666 Ext. 3276
Fax: (613) 548-1392
E-mail: wwanesth@kgh.kari.net
Web Site: http://meds.queensu.ca/whistler

TE WAI ORA
Nelson Marlborough
District Health Board

The Nelson Marlborough region, situated at the top of the South Island (New Zealand) is renowned for its outdoor and recreational opportunities, great wine, food and high sunshine hours. This is an excellent opportunity to combine a career and a lifestyle. NMDHB has 2 base hospitals, Nelson and Wairau (situated in Blenheim). We provide a wide range of services to a population base of approximately 120,431.

These regional positions offer an exciting future, in one of the world's premier wine regions.

Applicants are required to hold vocational registration or be eligible for registration in New Zealand as a Specialist with registration eligibility verified at the time of applying.

Specialist Anaesthetist

Here is an opportunity for a part-time (32 hrs / week negotiable) Anaesthetist with appropriate qualifications to become part of a team of 4 Anaesthetists at Wairau Hospital. You may be required to work at Nelson Hospital as part of a regional anaesthesia service.

You will be required to carry out pre and postoperative assessments, anaesthesia for surgical lists and other procedures requiring anaesthesia. An Epidural Service is provided in Obstetrics. A private surgical facility provides additional opportunity for private practice.

For further information please contact Mark Robertson, Clinical Director for the Anaesthetic Department at mark.robertson@nmhs.govt.nz

Closing date: 27 October 2002. Reference w2002/73

For an application form and job description for the above positions, please contact the Human Resources Department, Wairau Hospital, PO Box 46, Blenheim, New Zealand, telephone +64 3577 1919, fax +64 3 577 1932 or email julie.gapper@nmhs.govt.nz.

www.nmdhb.govt.nz

JOURNAL ADVERTISING

To advertise in this publication contact

PRC
ASSOCIATES
Advertisement Managers

PRC ASSOCIATES LTD
THE ANNEXE, FITZNELLS MANOR
CHESSINGTON ROAD, EWELL VILLAGE, SURREY KT17 1TF, UK
TELEPHONE: +44 (0)20 8786 7376 FAX: +44 (0)20 8786 7262
EMAIL: mail@prcassoc.co.uk

JA
International Journal of Anaesthesia

Volume 89 Number 4 October 2002

EDITORIALS

535 I. Intraperitoneal administration of analgesia: is this practice of any utility?
A. Ng and G. Smith

537 II. Should we demand fresh red blood cells for perioperative and critically ill patients?
S. A. McLellan, T. S. Walsh and D. B. L. McClelland

CLINICAL INVESTIGATIONS

541 Comparison of two techniques for measuring penetration of sodium chloride particles through breathing system filters
A. R. Wilkes

546 Xenon has no effect on cytokine balance and adhesion molecule expression within an isolated cardiopulmonary bypass system
A. Bedi, W. T. McBride, M. A. Armstrong, J. M. Murray and J. P. H. Fee

551 Comparison of ocular microtremor and bispectral index during sevoflurane anaesthesia
L. G. Kevin, A. J. Cunningham and C. Bolger

556 Randomized, double-blind comparison of different inspired oxygen fractions during general anaesthesia for Caesarean section
W. D. Ngan Kee, K. S. Khaw, K. C. Ma, A. S. Y. Wong and B. B. Lee

562 Epinephrine and clonidine do not improve intrathecal sufentanil analgesia after total hip replacement
R. Fournier, E. Van Gessel, A. Weber and Z. Gamulin

567 Remifentanil compared with sufentanil during extra-corporeal shock wave lithotripsy with spontaneous ventilation: a double-blind, randomized study
H. Beloeil, G. Corsia, P. Coriat and B. Riou

571 Phenotyping malignant hyperthermia susceptibility by measuring halothane-induced changes in myoplasmic calcium concentration in cultured human skeletal muscle cells
T. Girard, S. Treves, K. Censier, C. R. Mueller, F. Zorzato and A. Urwyler

580 Pharmacodynamics of mivacurium chloride in 13- to 18-yr-old adolescents with thermal injury
J. A. J. Martyn, Y. Chang, N. G. Goudsouzian and S. S. Patel

586 Training course in local anaesthesia of the airway and fibreoptic intubation using course delegates as subjects
V. Patil, G. L. Barker, R. J. Harwood and N. M. Woodall

594 Evaluation of effects of magnesium sulphate in reducing intraoperative anaesthetic requirements
L. Telci, F. Esen, D. Akcora, T. Erden, A. T. Canbolat and K. Akpir

LABORATORY INVESTIGATIONS

599 Haemodynamic effects of an angiotensin-converting enzyme inhibitor and angiotensin receptor antagonist during hypovolaemia in the anaesthetized pig
F. Ryckwaert, P. Colson, E. André, P.-F. Perrigault, G. Guillon and C. Barberis

605 Apparent diffusion coefficient mapping predicts mortality and outcome in rats with intracerebral haemodynamic disturbance: potential role of intraoperative diffusion and perfusion weighted magnetic resonance imaging to detect cerebral ischaemia
S. Ishikawa, K. Yokoyama, T. Kuroiwa and K. Makita

614 Mechanisms of action of midazolam on expression of contextual fear in rats
L. Pain, A. Launoy, N. Fouquet and P. Oberling

REVIEW ARTICLE

622 Pathophysiology and clinical implications of perioperative fluid excess
K. Holte, N. E. Sharrock and H. Kehlet

SHORT COMMUNICATIONS

633 Root-cause analysis of an airway filter occlusion: a way to improve the reliability of the respiratory circuit
P. Garnerin, E. Schiffer, E. Van Gessel and F. Clergue

635 Saliva cyclic GMP increases during anaesthesia
T. Engelhardt, H. F. Galley, F. M. MacLennan and N. R. Webster

637 Remifentanil or propofol for sedation during carotid endarterectomy under cervical plexus block
H. Krenn, E. Deusch, H. Jellinek, W. Oczenski and R. D. Fitzgerald

CASE REPORTS

641 Spontaneous breathing combined with high frequency ventilation during bronchoscopic resection of a large tracheal tumour
M. Satoh, Y. Hirabayashi and N. Seo

644 Postoperative use of a cough-assist device in avoiding prolonged intubation
W. A. Marchant and R. Fox

647 Bilateral pleural effusions: unexpected complication after left internal jugular venous catheterization for total parenteral nutrition
H. G. W. Paw

650 The stuck central venous catheter: beware of potential hazards
S. Mahadeva, A. Cohen and M. Bellamy

652 Use of implantable cardioverter defibrillator and anti-arrhythmic agents in a parturient
A. J. Olufolabi, G. A. Charlton, S. A. Allen, I. M. Mettam and P. R. Roberts

655 Anaesthetic management of severe bradycardia during general anaesthesia using temporary cardiac pacing
V. Toprak, A. Yentur and M. Sakarya

658 CORRESPONDENCE

664 BOOK REVIEWS

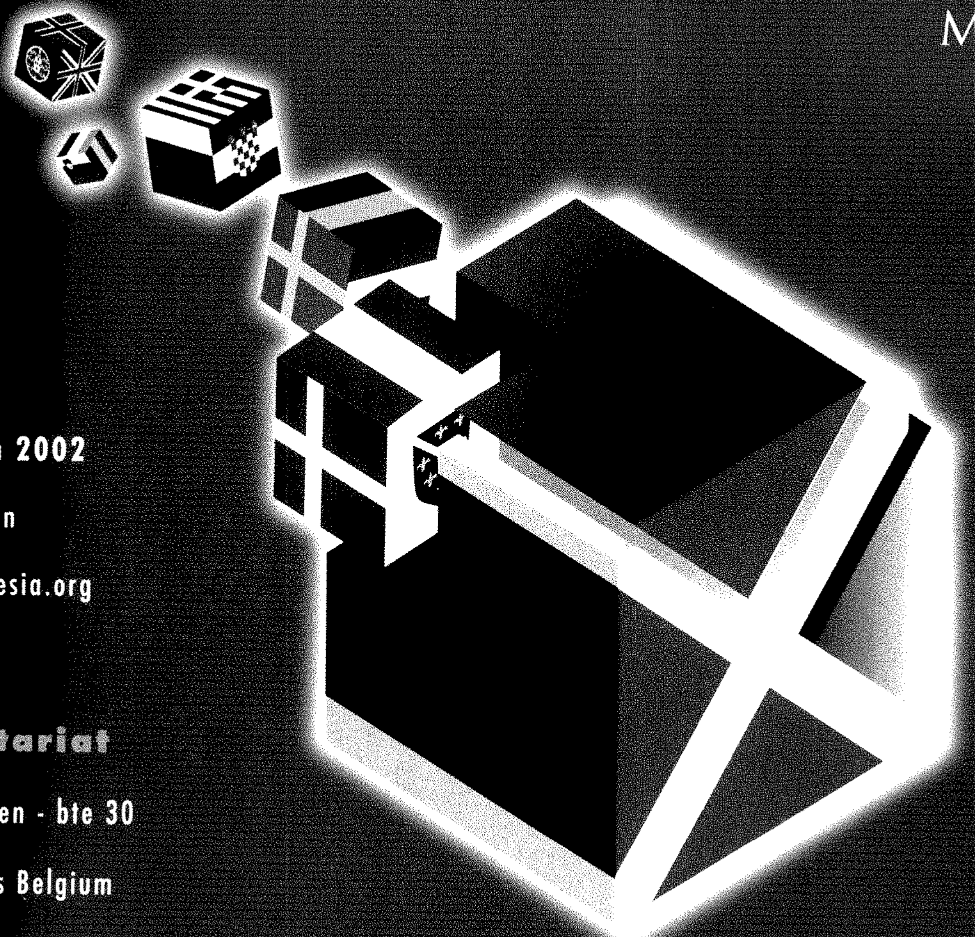
669 ERRATUM

ABSTRACTS

670P Proceedings of the Anaesthetic Research Society Meeting, Cardiff Meeting, July 11–12, 2002

Joint Meeting of the
European Society of Anaesthesiologists
European Academy of Anaesthesiology
Confederation of European National Societies of Anaesthesiology
Association of Anaesthetists of Great Britain & Ireland

Glasgow
Scotland
Euroanaesthesia
2003
MAY31-JUNE3



Deadline abstracts:
December 15th 2002
Online submission
www.euroanesthesia.org

ESA Secretariat
32 Av. de Tervuren - bte 30
B-1040 Bruxelles Belgium
Phone +32 (0) 2 743 32 90
Fax +32 (0) 2 743 32 98
E-mail: secretariat.esa@euronet.be

Symposia
Refresher Courses
Workshops
Industrial Symposia
& Exhibition
Free Presentations

AMA Category 1
CME Accreditation

Editorial Board

Editor-in-Chief

JENNIFER M. HUNTER, Professor of Anaesthesia, *University of Liverpool*

Editors

G. B. DRUMMOND, Senior Lecturer in Anaesthesia, *Royal Infirmary, Edinburgh*
P. M. HOPKINS, Professor of Anaesthesia, *University of Leeds*
D. G. LAMBERT, Reader in Anaesthetic Pharmacology, *University of Leicester*
D. J. ROWBOTHAM, Professor of Anaesthesia and Pain Management, *University of Leicester*

Board Members

F. BONNET, Professor of Anaesthesia, *Assistance Publique Hopitaux de Paris*
H. F. GALLEY, Senior Lecturer in Anaesthesia and Intensive Care, *University of Aberdeen*
G. M. HALL, Professor of Anaesthesia, *University of London*
S. J. HOWELL, Senior Lecturer in Anaesthesia, *University of Leeds*
P. HUTTON, President, *Royal College of Anaesthetists*
D. M. JUSTINS, Vice-president, *Royal College of Anaesthetists*
P. A. LONNQVIST, Associate Professor of Paediatric Anaesthesia and Intensive Care, *Lingrens Children's Hospital, Stockholm, Sweden*
R. D. MILLER, Professor of Anesthesia, *University of California, San Francisco*
I. POWER, Professor of Anaesthesia, Critical Care and Pain Medicine, *University of Edinburgh*
H.-J. PRIEBE, Professor of Anaesthesia, *University of Freiburg, Germany*
C. S. REILLY (Treasurer), Professor of Anaesthesia, *University of Sheffield*
J. W. SEAR, Professor of Anaesthesia, *University of Oxford*
P. J. SIMPSON, Vice-president, *Royal College of Anaesthetists*
G. SMITH (Chairman), Professor of Anaesthesia, *University of Leicester*
J. R. SNEYD, Professor of Anaesthesia, *University of Plymouth*
D. R. SPAHN, Professor of Anaesthesia, *University Hospital, Lausanne, Switzerland*
N. R. WEBSTER (Secretary), Professor of Anaesthesia, *University of Aberdeen*
J. A. W. WILDSMITH, Professor of Anaesthesia, *Ninewells Hospital and Medical School, Dundee*
J. D. YOUNG, Reader in Anaesthesia, *Radcliffe Infirmary, Oxford*

International Board Members

F. CARLI, Wesley Bourne Professor and Chairman, Department of Anesthesia, *McGill University, Montreal, Canada*
K. HIROTA, Department of Anesthesiology, *University of Hirosaki, Japan*

Assistant Editors

R. S. JONES, Professor of Veterinary Anaesthesia, *University of Liverpool*
B. V. S. MURTHY, Consultant Anaesthetist, *Royal Liverpool University Hospital*

Production Staff

E. GOODING, Senior Production Editor, *Oxford University Press*
H. J. LAMB, Production Editor, *Oxford University Press*
G. G. R. T. MUCKLOW, Editorial Assistant, *Oxford University Press*
Please visit the Journals's World Wide Web site at http://bja.oupjournals.org

University College of Medicine LIBRARY

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

General Information

Subscriptions

All Fellows of the College, world-wide, should notify changes of address directly to the Royal College of Anaesthetists.

An annual subscription to *BJA* comprises 12 issues (two volumes of 6 issues), with Author and Subject Indexes. Subscriptions are entered on a calendar year basis only. Please add local sales tax to the prices quoted. Prices include postage by surface mail, or for subscribers in the USA and Canada by Airfreight, or in Japan, Australia, New Zealand, and India by Air Speeded Post. Airmail rates are available on request.

Annual subscription rate 2002
Full text print version of the *BJA*
Full rate (institutions and individuals): UK and Europe £255, Rest of World US$400
Trainees: UK and Europe £120, Rest of World US$190
ESA/EACTA/EAA/ESRA/JSA/IARS members: UK and Europe £120, Rest of the World US$190
Single issue: UK and Europe £27, Rest of World US$38

Orders

Orders and payments from, or on behalf of, subscribers in the various geographical areas shown below should be sent to the office indicated. Payment may be made by the following methods: cheque (made payable to Oxford University Press); National Girobank (Account 500 1056); credit card (Mastercard, Visa, American Express); UNESCO coupons; direct debit (please ask for details). Bankers: Barclays Bank plc, PO Box 333, Oxford, UK; Code 20-65-18; Account 00715654.

The Americas: Oxford University Press Inc., 2001 Evans Road, Cary, NC 27513, USA.

Japan: available from the following agents:

Kinokuniya Company Ltd, Journal Department, PO Box 55, Chitose, Tokyo, 156 Japan.
Maruzen Company Ltd, Journal Division, PO Box 5050, Tokyo International, 100-31 Japan.
Usaco Corporation, 13-12 Shimbashi 1-chome, Minato-ku, Tokyo, 105 Japan.

Rest of the world: Oxford University Press, Journals Subscriptions Department, Great Clarendon Street, Oxford OX2 6DP, UK. Tel +44 (0)1865 267907; Fax: +44 (0)1865 267485; E-mail: jnl.orders@oup.co.uk

Please address orders and enquiries about availability as follows: *For current volume and back numbers from Vol. 82 onwards* to Oxford University Press. *For Vols 1-81* to Periodicals Service Company, 11 Main Street, Germantown, NY 12526, USA.
Tel: +1 (518) 537 4700; Fax: +1 (518) 537 5899.

Advertising

Advertising enquiries should be addressed to Peter Carpenter, PRC Associates, The Annexe, Fitznells Manor, Chessington Road, Ewell Village, Surrey KT17 1TF, UK.
Tel: +44 (0)20 8786 7376; Fax: +44 (0)20 8786 7262;
E-mail: mail@prcassoc.co.uk

© *The Board of Management and Trustees of the British Journal of Anaesthesia 2002*

All rights reserved; no part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise without the prior written permission of the *British Journal of Anaesthesia*, requests for which should be addressed to the Publisher, or a licence permitting restricted copying issued in the UK by the Copyright Licensing Agency Ltd, 90 Tottenham Court Road, London W1P 9HE, or in the USA by the Copyright Clearance Center, 222 Rosewood Drive, Danvers, MA 01923. For those in the US/Canada not registered with CCC, articles can be obtained by fax in 48 hours by calling: WISE for MedicineTM 1-800-667-WISE.

British Journal of Anaesthesia (ISSN 0007-0912) is published monthly by Oxford University Press, Oxford, UK. Annual subscription price is US$400. *British Journal of Anaesthesia* is distributed by Mercury International, 365 Blair Road, Avenel, NJ 07001, USA. Periodicals postage paid at Rahway, New Jersey, and additional entry points.

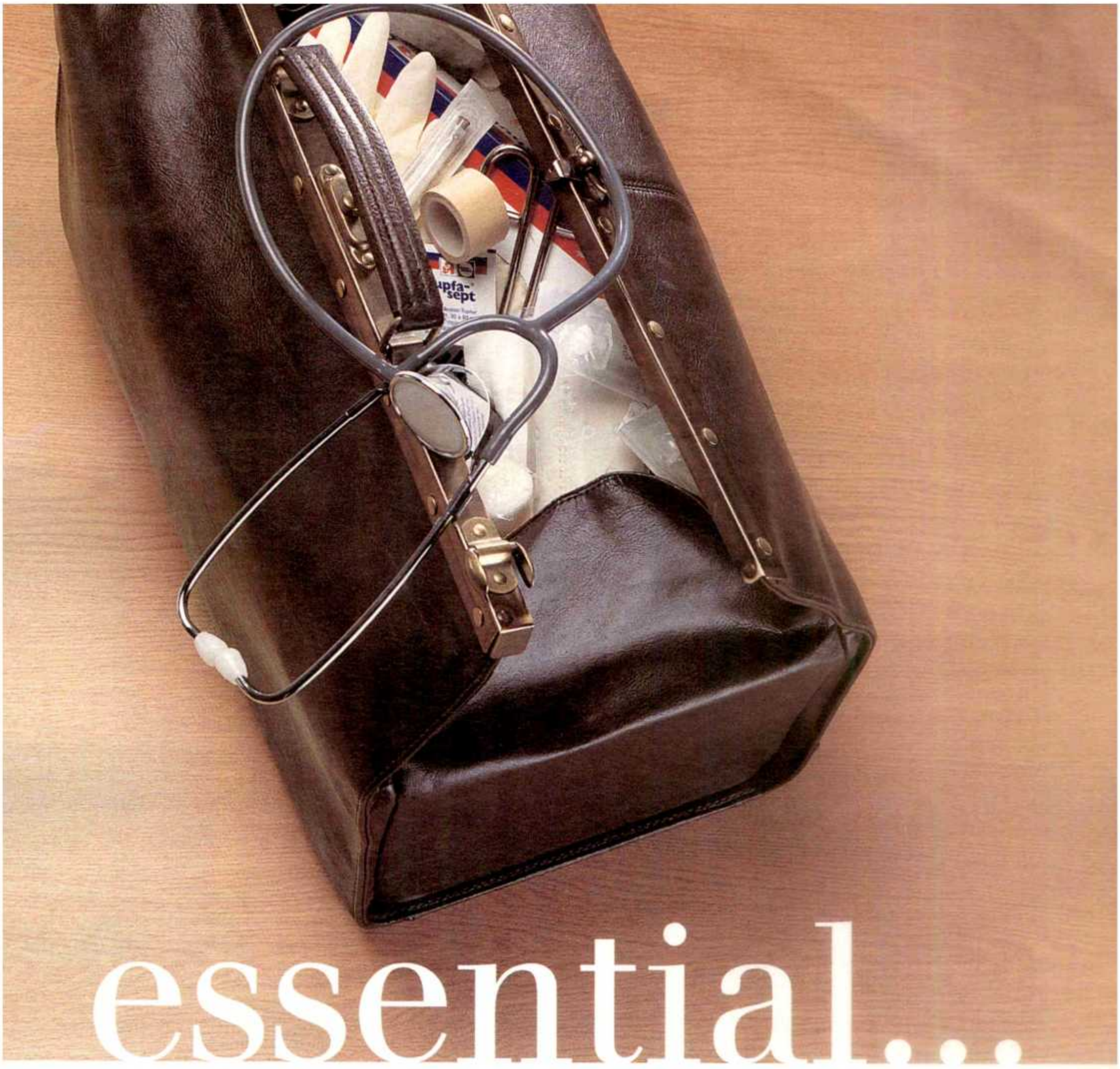
US Postmaster: send address changes to *British Journal of Anaesthesia*, c/o Mercury International, 365 Blair Road, Avenel, NJ 07001, USA.

Disclaimer

Whilst every effort is made by the publishers and editorial committee to see that no inaccurate or misleading data, opinions or statements appear in this Journal, they wish to make it clear that the data and opinions appearing in the articles and advertisements herein are the responsibility of the contributor or advertiser concerned. Accordingly, the publisher and the editorial committee and their respective employees, officers and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinions or statements. While every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described within this Journal, should only be followed in conjunction with the drug manufacturer's own published literature.

Printed by Information Press Ltd, Oxford, UK.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002



essential...

Editorial Notices

Important Notice to Authors

Electronic Submission of New Manuscripts to *The British Journal of Anaesthesia*

Please note that, from January 2003, the Editorial team requests that all new manuscripts (excluding Letters to the Editor and Book Reviews) be submitted electronically to the *British Journal of Anaesthesia* web site at: http://bja.manuscriptcentral.com

Clear instructions for submission of new manuscripts are available on this web site. If these instructions are not adhered to, difficulty will be experienced in submitting new articles. For an interim period, manuscripts may also be submitted as hard copy to the Editor-in-Chief's office. It is envisaged, however, that this arrangement will be discontinued by the end of 2003.

Jennifer M. Hunter
Editor-in-Chief

Royal Medical Benevolent Fund

Are you a current or very recently retired doctor? Would you like to help colleagues less fortunate than yourself? Our recent cases include doctors who have suffered strokes, cancer, multiple sclerosis, paralysis after serious road accidents, blindness, schizophrenia, manic depression, dependency and the suicide of a partner. A growing number are junior doctors with limited pension entitlement and insurance cover.

Do you have a few hours to help?

Medical Liason Officer

The aim is to ensure doctors and their families in your area are aware of the financial help which may be available from the RMBF in time of crisis, and in particular to:

- Liaise with local hospitals, medical centres, medical societies and associations, to seek to ensure that doctors and their families are aware of the type of help the Fund may be able to provide.
- To provide information about the RMBF to any colleagues and their dependants likely to need assistance and to advise the Fund where appropriate.
- To advise the Fund of any planned medical conferences, exhibitions or meetings in your area where it might be possible for the RMBF to be represented.

We need career grade doctors who are currently practising or very recently retired (i.e. within the last two years), with good contacts within the medical world and able to commit on average a couple of hours a week to help the Fund.

For further information about becoming a volunteer Medical Liaison Officer for the Fund, please contact: Royal Medical Benevolent Fund, 24 King's Road, Wimbledon, London SW19 8QN. Tel: +44 (0)208 540 9194; E-mail: info@rmbf.org

Help!

Have you had a patient showing signs of hypoxic brain damage when the Holmann laser was used, or urea renal stones and the oxygen alarm did not sound? If so, please contact:

Dr P. A. Charlebois, 2425 Eglinton Avenue East, Scarborough, Ontario, Canada.

Final FRCA Revision Course

Clinical Education Centre, Leicester Royal Infirmary, October 1–4, 2002

An intensive revision course of lectures, tutorials MCQ and SAQ papers and VIVA practice with individual feedback.

For further information, please contact: Christine Gethins. Tel: 0116 258 5291; E-mail: anae@le.ac.uk

Dingle 2002—4th Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 2–6, 2002

For further information contact: Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Crosspiece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

5th SW Thames Anaesthesia Forum

Da Balaia, The Algarve, Portugal, October 7–10, 2002

The scientific programme will include lectures and discussions on: acute and chronic pain; paediatric update; obstetric anaesthesia; neurology and anaesthesia; ITU and relevant medical topics; cardiothoracic anaesthesia; day case surgery; regional blocks; new drugs update; and training and education. There will be free papers; core topics for personal portfolio, guest speakers, workshops, videos on new drugs, equipment and techniques.

Open to all anaesthetists. Anaesthetists in training presenting papers are eligible for prizes. Deadline for abstracts: August 24, 2002. Meeting approved for CME. For full information and for online registration please visit: www.doctorsupdates.com

Dr J. B. Liban, Anaesthetic Department, St George's Hospital, Blackshaw Road, London SW17 0QT, UK. Tel: +44 (0) 208 725 3135; E-mail: liban@mailbox.co.uk

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

MEDICA®

Visit our booth
November 20.–23., 2002
Düsseldorf, Germany
Hall 11 / 11 J 39

Out on call. All the essentials in the doctor's bag. In the OR. All the essentials from Primus. Dräger Medical's next-generation anesthesia workstation is designed to be your personal anesthesia assistant in the most demanding operations and in everyday clinic routine. With its advanced software Primus supports your decision-making for improved efficiency in low-flow delivery and parameter-setting. Primus also sets new standards in perioperative therapy with its new, innovative Intensive Care ventilator performance. A modular design, open-platform architecture and individual upgrade packages ensure you get a customized personal assistant to meet your specific requirements, with the patient monitoring system of your choice. Primus allows you to enjoy optimized processes in the perioperative environment.

Primus is one of *three* pillars of innovation that mark a revolutionary new chapter in Dräger Medical's anesthesia device technology.

The essence of anesthesia.

Dräger
MEDICAL

NEW for the relief of pain a

ꓤCOXIA® (etoricoxib)
ƎRIDGED PRODUCT INFORMATION

er to Summary of Product Characteristics before prescribing.

SENTATION

ets: 60 mg, 90 mg and 120 mg tablets each containing 60 mg, 90 mg or 120 mg of etoricoxib ectively.

S

ptomatic relief of osteoarthritis, rheumatoid arthritis (RA) and the pain and signs of ammation associated with acute gouty arthritis.

SAGE AND ADMINISTRATION

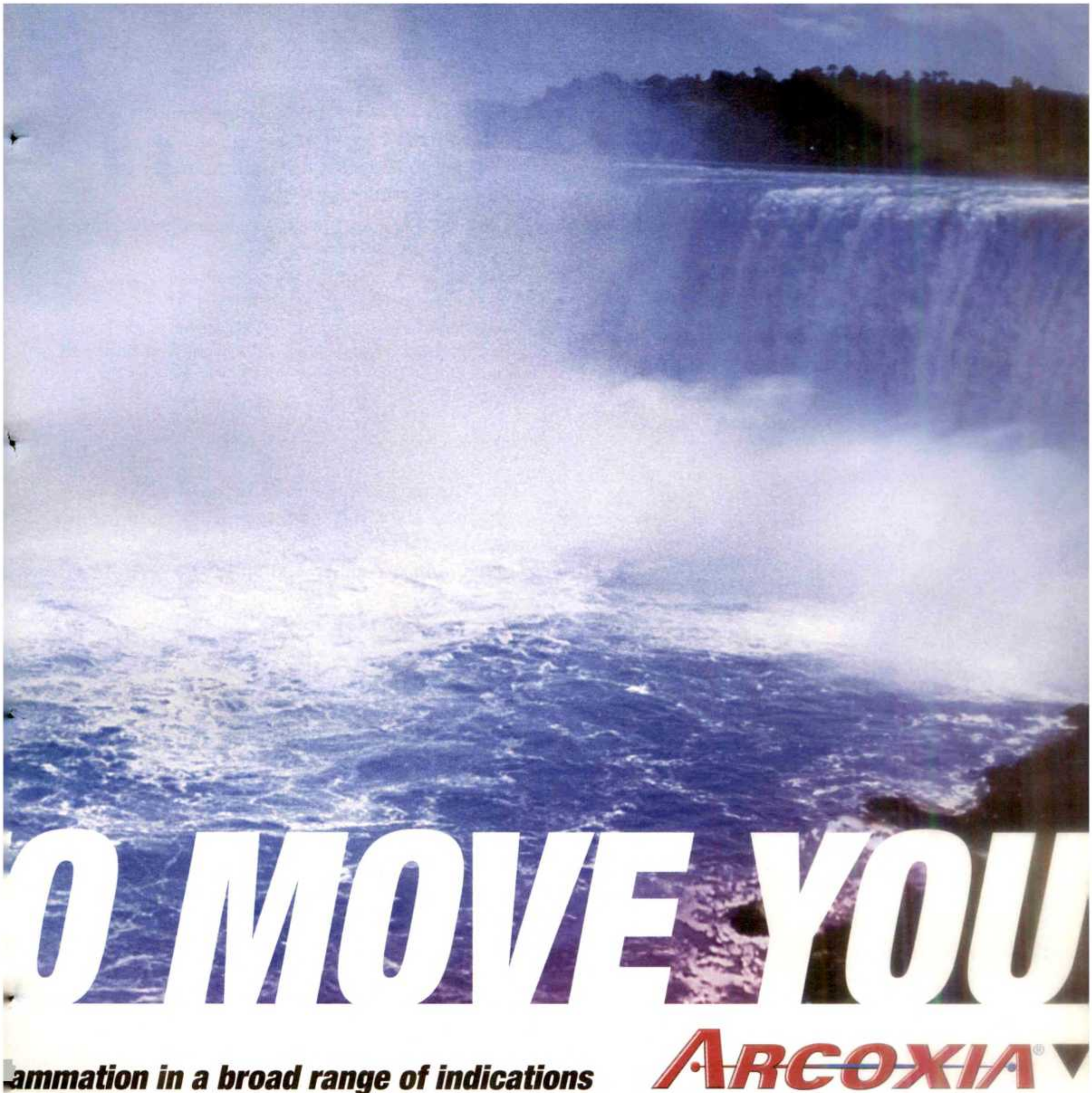
orally with or without food. Onset of action may be faster when administered without , and should be considered when rapid relief is needed. *Osteoarthritis:* 60 mg once daily. *umatoid arthritis:* 90 mg once daily. *Acute gouty arthritis:* 120 mg once daily for the acute ptomatic period only. Each dose above is the maximum recommended dose for each lition. *Renal insufficiency:* No dosage adjustment necessary for patients with creatinine rance ≥30 ml/min. *Hepatic insufficiency: mild* (Child-Pugh score 5-6): do not exceed a of 60 mg; *moderate* (Child-Pugh score 7-9): **do not exceed 60 mg every other day**.

NTRA-INDICATIONS

ersensitivity to any component of this product. Active peptic ulceration or gastro-intestinal bleeding. Severe hepatic dysfunction (Child-Pugh score >9). Estimated creatinine clearance ml/min. Patients who have developed signs of asthma, acute rhinitis, nasal polyps, oneurotic oedema or urticaria after aspirin or other NSAIDs. Pregnancy and lactation. Children and adolescents under 16 years of age. Inflammatory bowel disease. Severe congestive heart failure.

PRECAUTIONS

Cardiovascular: COX-2-selective inhibitors are not a substitute for aspirin for cardiovascular prophylaxis due to their lack of effect on platelets. Because etoricoxib does not inhibit platelet aggregation, do not discontinue antiplatelet therapies and if indicated, consider them in patients at risk for or with a history of cardiovascular or other thrombotic events. Exercise caution in patients with a medical history of ischaemic heart disease. Take appropriate measures and consider discontinuing etoricoxib therapy if there is clinical evidence of symptomatic deterioration in the condition of these patients. Lack of antiplatelet activity should also be considered in patients with a history of cerebrovascular disease. *Renal effects:* Consider monitoring renal function in patients with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis. *Fluid retention, oedema and hypertension:* Exercise caution in patients with a history of cardiac failure, left ventricular dysfunction, or hypertension and pre-existing oedema from any other reason, as fluid retention and oedema have been observed in patients taking etoricoxib. Take appropriate measures, including discontinuation of etoricoxib where there is clinical evidence of deterioration in the condition of these patients. *Gastro-intestinal effects:* In clinical studies, some patients treated with etoricoxib, developed perforations, ulcers or bleeds (PUBs). Independent of treatment, patients with a history of GI perforation, ulcers and bleeding and those aged greater than 65 years are known to be at higher risk of a PUB. *Hepatic effects:* Elevations of ALT and/or AST (>3 times the upper limit of normal) have been reported in approximately 1% of patients treated in trials with etoricoxib 60 mg and 90 mg for up to one year. Monitor any patient with symptoms/signs of liver dysfunction or in whom an abnormal liver function test has occurred. Discontinue etoricoxib if signs of he insufficiency occur, or if persistently abnormal liver function tests (3 times the upper lin normal) are detected. *General:* Maintain appropriate medical supervision when treatin elderly and patients with renal, hepatic or cardiac dysfunction with etoricoxib. Use caution initiating treatment in patients with considerable dehydration. Rehydrate patients prior to sta therapy with etoricoxib. Etoricoxib may mask fever. Use of etoricoxib is not recommend women attempting to conceive. *Interactions (pharmacodynamic): Oral anticoagulants:* cl monitor the prothrombin time INR when therapy with etoricoxib is initiated or the dose cha in patients receiving oral anticoagulants or similar agents, particularly in the first few *Diuretics and ACE-inhibitors:* NSAIDS may reduce the effect of diuretics and antihyperte drugs. In some patients with compromised renal function, the co-administration of an inhibitor and cyclo-oxygenase inhibitors may result in further deterioration of renal func which is usually reversible. *Aspirin:* etoricoxib can be used concomitantly with aspirin at used for cardiovascular prophylaxis (low dose aspirin). However, concomitant administr of low dose aspirin with etoricoxib may result in an increased rate of GI ulceration or complications compared to use of etoricoxib alone. Concomitant administration of etoric with doses of aspirin **above** those for cardiovascular prophylaxis, or with other NSAIDS recommended. *Cyclosporin/tacrolimus:* monitor renal function when etoricoxib and cyclosporin or tacrolimus is used in combination. *Interactions (pharmacokinetic) The of etoricoxib on the pharmacokinetics of other drugs: Lithium:* the plasma concentrati lithium is increased by NSAIDS, therefore monitor and adjust blood lithium and lithium d if necessary. *Methotrexate:* adequate monitoring is recommended for methotrexate-re toxicity when etoricoxib and methotrexate are administered concomitantly. *Oral Contrace (OC):* Administration of etoricoxib 120 mg with an OC containing 35 mcg ethinyl estr



ammation in a broad range of indications

ARCOXIA®

etoricoxib

ıd 0.5 to 1 mg norethindrone for 21 days, either concomitantly or separated by 12 hours, ed the steady state $AUC_{0\text{-}24hr}$ of EE by 50 to 60%; however, norethindrone concentrations lly did not increase to a clinically relevant degree. Consider this increase in EE tration when selecting an oral contraceptive for use with etoricoxib. *Digoxin:* Patients risk of digoxin toxicity should be monitored for an increase in digoxin C_{max} when xib and digoxin are administered concomitantly. *Effect of etoricoxib on drugs metabolised otransferases:* Etoricoxib is an inhibitor of human sulfotransferase activity, particularly E1 and has been shown to increase the serum concentrations of ethinyl estradiol. It may lent to exercise care when administering etoricoxib concurrently with other drugs primarily lised by human sulfotransferases (e.g. oral salbutamol and minoxidil). *Effect of etoricoxib gs metabolised by CYP isoenzymes:* Based on *in vitro* studies, etoricoxib is not expected oit cytochromes P450 (CYP) 1A2, 2C9, 2C19, 2D6, 2E1 or 3A4. In a study in healthy s, daily administration of etoricoxib 120 mg did not alter hepatic CYP3A4 activity as d by the erythromycin breath test. *Effects of other drugs on the pharmacokinetics of xib:* The main pathway of etoricoxib metabolism is dependent on CYP enzymes. CYP3A4 s to contribute to the metabolism of etoricoxib *in vivo*. *Ketoconazole:* a potent inhibitor P3A4, dosed at 400 mg once a day for 11 days to healthy volunteers did not have any ly important effect on the single-dose pharmacokinetics of 60 mg etoricoxib (43% increase). *Rifampicin:* Co-administration of etoricoxib with rifampicin, a potent inducer of CYP es, produced a 65% decrease in etoricoxib plasma concentrations, an interaction which sult in recurrence of symptoms. *Antacids:* Antacids do not affect the pharmacokinetics icoxib to a clinically relevant extent. *Pregnancy:* contra-indicated in the first, second rd trimesters of pregnancy. *Lactation:* contra-indicated.

SIDE EFFECTS

In clinical studies the following undesirable effects were reported at an incidence greater than placebo in patients with OA, RA or chronic low back pain treated with etoricoxib 60 mg or 90 mg for up to 12 weeks: *[Common (>1/100, <1/10) Uncommon (>1/1000, <1/100) Rare (>1/10,000, <1/1,000)]*

Infections and infestations: *Uncommon:* gastro-enteritis, upper respiratory infection, urinary tract infection. ***Immune system disorder:*** *Very rare:* drug hypersensitivity. ***Metabolism and nutrition disorders:*** *Uncommon:* appetite increase or decrease, oedema/fluid retention, weight gain. ***Psychiatric disorders:*** *Uncommon:* anxiety, depression, mental acuity decreased. ***Nervous system disorder:*** *Common:* dizziness, headache. *Uncommon:* dysgeusia, insomnia, paraesthesia/hypaesthesia, somnolence. ***Eye disorders:*** *Uncommon:* blurred vision. ***Ear and labyrinth disorders:*** *Uncommon:* tinnitus. ***Cardiac disorders:*** *Uncommon:* congestive heart failure, non-specific ECG changes. *Very rare:* myocardial infarction. ***Vascular disorders:*** *Uncommon:* flushing, hypertension. *Very rare:* cerebrovascular accident. ***Respiratory, thoracic and mediastinal disorders:*** *Uncommon:* cough, dyspnoea, epistaxis. ***Gastro-intestinal disorders:*** *Common:* gastro-intestinal disorders (e.g. abdominal pain, flatulence, heartburn), diarrhoea, dyspepsia, epigastric discomfort, nausea. *Uncommon:* abdominal distention, acid reflux, bowel movement pattern change, constipation, dry mouth, gastroduodenal ulcer, irritable bowel syndrome, oesophagitis, oral ulcer, vomiting. *Very Rare:* gastro-intestinal perforation and bleeding. ***Skin and subcutaneous tissue disorders:*** *Uncommon:* ecchymosis, facial oedema, pruritus, rash. ***Musculoskeletal, connective tissue and bone disorders:*** *Uncommon:* muscular cramp/spasm, musculoskeletal pain/stiffness. ***Renal and urinary disorders:*** *Uncommon:* proteinuria. ***General disorders and administration site conditions:*** *Common:* asthenia/fatigue, flu-like disease. *Uncommon:* chest pain. ***Investigations:*** *Common:* ALT increased, AST increased. *Uncommon:* blood urea nitrogen increased, creatine phosphokinase increase haematocrit decreased, haemoglobin decreased, hyperkalaemia, leukocytes decreased, platelc decreased, serum creatinine increased, uric acid increased. The following serious undesirab effects have been reported in association with the use of NSAIDs and cannot be ruled out f etoricoxib: nephrotoxicity including interstitial nephritis and nephrotic syndrome and ren failure; hepatotoxicity including hepatic failure and jaundice; cutaneo-mucosal adverse effec and severe skin reactions.

PACKAGE QUANTITIES AND BASIC NHS COST

60 and 90 mg Tablets: packs of 28 tablets £22.96; 120 mg Tablets: packs of 7 tablets £5.7

Marketing Authorisation numbers

Tablet 60 mg PL 0025/0422; Tablet 90 mg PL 0025/0423; Tablet 120 mg PL 0025/0424.

Marketing Authorisation holder

Merck Sharp & Dohme Limited, Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, U

POM **Date of review:** July 2002

® denotes registered trademark of Merck & Co., Inc., Whitehouse Station, NJ, USA.

© Merck Sharp & Dohme Limited 2002. All rights reserved.

MSD

Merck Sharp & Dohme Limited

Hertford Road, Hoddesdon, Hertfordshire EN11 9BU

International Society for Anaesthetic Pharmacology (ISAP, formerly SIVA)

Orlando, Florida, USA, October 11, 2002

Contact: International Society for Anaesthetic Pharmacology (ISAP), 2 Summit Park Drive, Suite 140, Cleveland, OH 44131-2553, USA. Tel: +1 216 447 7862; Fax: +1 216 642 1127; E-mail: isaphq@iars.org; Website www.isaponline.org

Australian Society of Anaesthetists National Scientific Congress

Adelaide, Australia, October 26–30, 2002

This is the Society's premier scientific conference, held in an interesting part of the world.

For further details, please contact: Festival City Conventions, PO Box 949, Kent Town, SA 5071, Australia. Tel: +61 (0)8 8363 1307; Fax: +61 (0)8 8363 1604: E-mail: asa2002@fccconventions.com.au

8th International Congress of Cardiothoracic and Vascular Anesthesia
19th International Congress of the Israel Society of Anesthesiologists

Jerusalem, Israel, November 10–13, 2002

For further information regarding the Congress, please contact:

8th International Congress of Cardiothoracic and Vascular Anesthesia, PO Box 50006, Tel Aviv 61500, Israel

Tel: +972 3 5140000; Fax: +972 3 5140077; E-mail: anesth2002@kenes.com

Web address: http://www.isranest.org.il/congress 2002

Primary FRCA Revision Course

Clinical Education Centre, Leicester Royal Infirmary, November 27–29, 2002

An intensive revision course with emphasis on small group tutorial teaching and including MCQ and VIVA practice with individual feedback.

For further information, please contact: Christine Gethins. Tel: 0116 258 5291; E-mail: anae@le.ac.uk

Liverpool Society of Anaesthetists Slim Volume Symposium: Evidence-based anaesthesia and critical care—a slim volume?

Moat House, Chester, UK, November 28–29, 2002

For further details, please contact: Georgina Hall, Department of Anaesthesia, Arrowe Park Hospital, Upton, Wirral, Merseyside CH49 5PE, UK. Tel: +44(0)151 604 7056; Fax: +44(0)151 604 7126; E-mail: georgina.hall@whnt.nhs.uk

Third Euro-PNB Winter Symposium: postgraduate course on peripheral nerve blockade in surgery and pain management for anaesthesiologists

Excelsior Mila Hotel, Crans-Montana, Switzerland, January 16–19, 2003

Meet European experts in this stimulating course and workshops in an exciting environment.

Registration before December 1, 2002 to: Assoc. Professor Alain Borgeat, Department of Anaesthesia and Intensive Care, Orthopedic University Clinic, Balgrist/Zürich, Forchstrasse 340, CH-8008 Zürich, Switzerland. Tel: +41 1 386 38 32; Fax: +41 1 386 16 09; E-mail: agorgeat@balgrist.unizh.ch

21st Annual Symposium: Clinical Update in Anesthesiology and Advances in Techniques of Cardiopulmonary Bypass with International Faculty and Industrial Exhibits

Antigua, West Indies, January 19–25, 2003

For information on abstracts, posters and free papers (deadline: November 4, 2002) please contact: Helen Phillips, Mount Sinai Medical Centre, 1 Gustave L. Levy Place, Box 1010, NY 10029-6574, USA. Tel: +1 212 241 7467; Fax: +1 212 426 2009; E-mail: helen.phillips@mssm.edu

77th Clinical and Scientific Congress of the International Anesthesia Research Society

New Orleans Marriott, New Orleans, Louisiana, March 22–26, 2003

For further information, please contact:

International Anesthesia Research Society, 2 Summit Park Drive, Suite 140, Cleveland, OH 44131-2553, USA. Tel: +1 216 642 1124; Fax: +1 216 642 1127; E-mail: iarshq@iars.org; Website: www.iars.org

Advances in Anatomy and Clinical Examination of the Hand and Wrist

Genval (Brussels), Belgium, March 28–29, 2003
Presymposium Hands-on Course of Hand Surgical Anatomy, March 27, 2003

The symposium will promote exchange between scientists and clinicians, and will include presentations by invited faculty. Participants may submit original papers for a limited number of oral presentations, and there will be considerable time reserved for discussion. Deadline for submission of abstracts: December 31, 2002.

For further details, please contact: F. Schuind, MD, PhD, Department of Orthopaedics, Erasme University Hospital, 808 route de Lennik, B-1070 Brussels, Belgium. Tel: +32 2

THE POWER TO RISE ABOVE PAIN
5mg
now available
IN MALIGNANCY AND POST-OPERATIVE PATIENTS
12-HOURLY
▼ OxyContin®
Prolonged release oxycodone hydrochloride tablets
www.napp.co.uk/pain password: 120012

A **REAL ADVANCE** IN OPIOID **ANALGESIA**

PRESCRIBING INFORMATION OxyContin®▼ 5 mg, 10 mg, 20 mg, 40 mg, 80 mg tablets United Kingdom **Presentation** Film-coated, prolonged release tablets containing oxycodone hydrochloride, marked OC on one side and the strength of oxycodone hydrochloride on the other. The 5 mg tablets are blue and contain 5 mg of oxycodone hydrochloride. The 10 mg tablets are white and contain 10 mg of oxycodone hydrochloride. The 20 mg tablets are pink and contain 20 mg of oxycodone hydrochloride. The 40 mg tablets are yellow and contain 40 mg of oxycodone hydrochloride. The 80 mg tablets are green and contain 80 mg of oxycodone hydrochloride. **Indications** For the treatment of moderate to severe pain in patients with cancer and post-operative pain. **Dosage and administration** OxyContin tablets must be swallowed whole, and not chewed. *Elderly and adults over 18 years:* OxyContin tablets should be taken at 12-hourly intervals. The dosage is dependent on the severity of the pain, and the patient's previous history of analgesic requirements. The usual starting dose for opioid naïve patients or patients presenting with severe pain uncontrolled by weaker opioids is 10 mg, 12-hourly. Some patients may benefit from a starting dose of 5 mg especially those with renal or hepatic impairment. If higher doses are necessary, increases should be made, where possible in 25% – 50% increments. Patients transferring from morphine should have the daily dose based on the following ratio: 10 mg oral oxycodone is equivalent to 20 mg oral morphine. For most patients the maximum dose of OxyContin tablets is 200 mg, 12-hourly. However, a few patients may require higher doses. Doses in excess of 1000 mg have been reported. *Children under 18 years:* Not recommended. **Contra-indications** Respiratory depression, head injury, paralytic ileus, acute abdomen, delayed gastric emptying, chronic obstructive airways disease, chronic bronchial asthma, hypercarbia, known oxycodone sensitivity, moderate to severe hepatic impairment, severe renal impairment, chronic constipation, concurrent administration of monoamine oxidase inhibitors or within 2 weeks of discontinuation of their use. Not recommended for pre-operative use or for the first 24 hours post-operatively. Pregnancy. **Precautions and warnings** A reduction in dosage may be advisable in hypothyroidism. Use with caution in opioid dependent patients and in patients with raised intracranial pressure, hypotension, hypovolaemia, toxic psychosis, diseases of the biliary tract, pancreatitis, inflammatory bowel disorders, prostatic hypertrophy, adrenocortical insufficiency, acute alcoholism, delirium tremens, chronic renal and hepatic disease, severe pulmonary disease and debilitated patients. OxyContin tablets should not be used where there is a possibility of paralytic ileus occurring. Should paralytic ileus be suspected or occur during use, OxyContin tablets should be discontinued immediately. Patients who are to undergo cordotomy or other pain relieving surgical procedures should not receive OxyContin tablets for 24 hours before surgery. If further treatment with OxyContin tablets is then indicated the dosage should be adjusted to the new post-operative requirement. OxyContin 80 mg should not be used in patients not previously exposed to opioids. OxyContin tablets should be used with caution following abdominal surgery, as opioids are known to impair intestinal motility and should not be used until the physician is assured of normal bowel function. OxyContin tablets must be swallowed whole and not broken, chewed or crushed. **Pregnancy and lactation** Not recommended. Oxycodone is secreted in breast milk and may cause respiratory depression in the newborn. OxyContin tablets should, therefore, not be used in breast-feeding mothers. **Side-effects** Adverse drug reactions are typical of full opioid agonists. Tolerance and dependence may occur. The most common adverse drug reactions seen during therapy are constipation, nausea, vomiting, dry mouth, anorexia, dyspepsia, abdominal pain, diarrhoea, headache, confusion, asthenia, faintness, dizziness, sedation, anxiety, abnormal dreams, nervousness, insomnia, thought abnormalities, drowsiness, twitching, orthostatic hypotension, bronchospasm, dyspnoea, decreased cough reflex, rash, pruritus, sweating, chills. **Legal category** CD (Sch2) POM **Package quantities and price** 5 mg – £10.72 (28 tablets) 10 mg – £21.43 (56 tablets) 20 mg – £42.86 (56 tablets) 740 mg – £85.73 (56 tablets) 80 mg – £171.46 (56 tablets) **Marketing Authorisation numbers** PL 16950/0097-0100, 0123 **Marketing Authorisation holder** Napp Pharmaceuticals Limited, Cambridge Science Park, Milton Road, Cambridge CB4 0GW UK. Tel: 01223 424444. Member of the Napp Pharmaceutical Group. Further information is available from Napp Pharmaceuticals Limited. **Date of preparation** May 2002. ®OxyContin and the NAPP device are Registered Trade Marks. ©Napp Pharmaceuticals Limited 2002. European Patent (UK) 0 253 104 European Patent (UK) 0 576 643. European Patent Application No. 96102992.3. **Date of preparation** May 2002.

A leader
NAPP
in pain control

555 68 44/36 45; Fax: +32 2 520 35 36; E-mail: Hand.congress@ulb.ac.be

German Congress of Anaesthesiology 2003

(DAK 2003)

München, April 9–13, 2003

For further information, please contact:

Medizinisch Congressorganization Nürnberg AG.
Tel: +49 911 393160; Fax: +49 911 331204

27th Congress of The Scandinavian Society of Anaesthesiology and Intensive Care Medicine

Helsinki, Finland, August 16–20, 2003

A biannually arranged Scandinavian congress in one of the five Scandinavian countries; language: English.

For further information please contact: Prof. Per H.Rosenberg, Helsinki University Hospital, Helsinki FIN00029 HUS, Finland.

E-mail: per.rosenberg@hus.fi
Or: CONGREX/Blue & White Conferences Oy
E-mail: congrex@congrex.fi
Web address: www.congrex.fi

Société Française d'Anesthésie et de Réanimation

Annual congresses will take place in Palais des Congrés, Porte Maillot, Paris on the following dates:

September 18–21, 2003
September 20–October 3, 2004
September 29–October 2, 2005

For further information, please contact: SFAR, 74, rue Raynouard, F-75016 Paris, France. Tel: +33 1 45 25 82 25; Fax: +33 1 40 50 35 22; E-mail SFAR@invivo.edu

Dingle 2003—5th Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 1–5, 2003

For further information contact:

Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Crosspiece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

7th Biennial Congress of the Asian and Oceanic Society of Regional Anesthesia and Pain Medicine

Bangkok, Thailand, November 5–8, 2003

A biennial congress with a scientific programme of special lectures, symposiums, and workshops on various techniques of regional anaesthesia and pain medicine.

For further information, please contact: AOSRA Secretariat, 39 Pradipat 10 (Phaholyothin 11) phyathai, Bangkok 10400, Thailand. Tel: +66 0 2615 7301; Fax: +66 0 2615 7309; Mobile: +66 (01) 836 1368; E-mail: cdm@cdmthailand.com

Web address: http://www.cdmthailand.com

13th World Congress of Anaesthesiologists

Palais des Congrès de Paris, Paris, France, April 18–23, 2004

For further details, please contact the Congress Office at: COLLOQUIUM, 12 rue de la Croix Faubin, F-75557 Paris cedex 11, France. Tel: +33 (0) 1 44 64 15 15. Fax: +33 (0) 1 44 64 15 16/17. E-mail: wca2004@colloquium.fr Website: www.wca2004.com

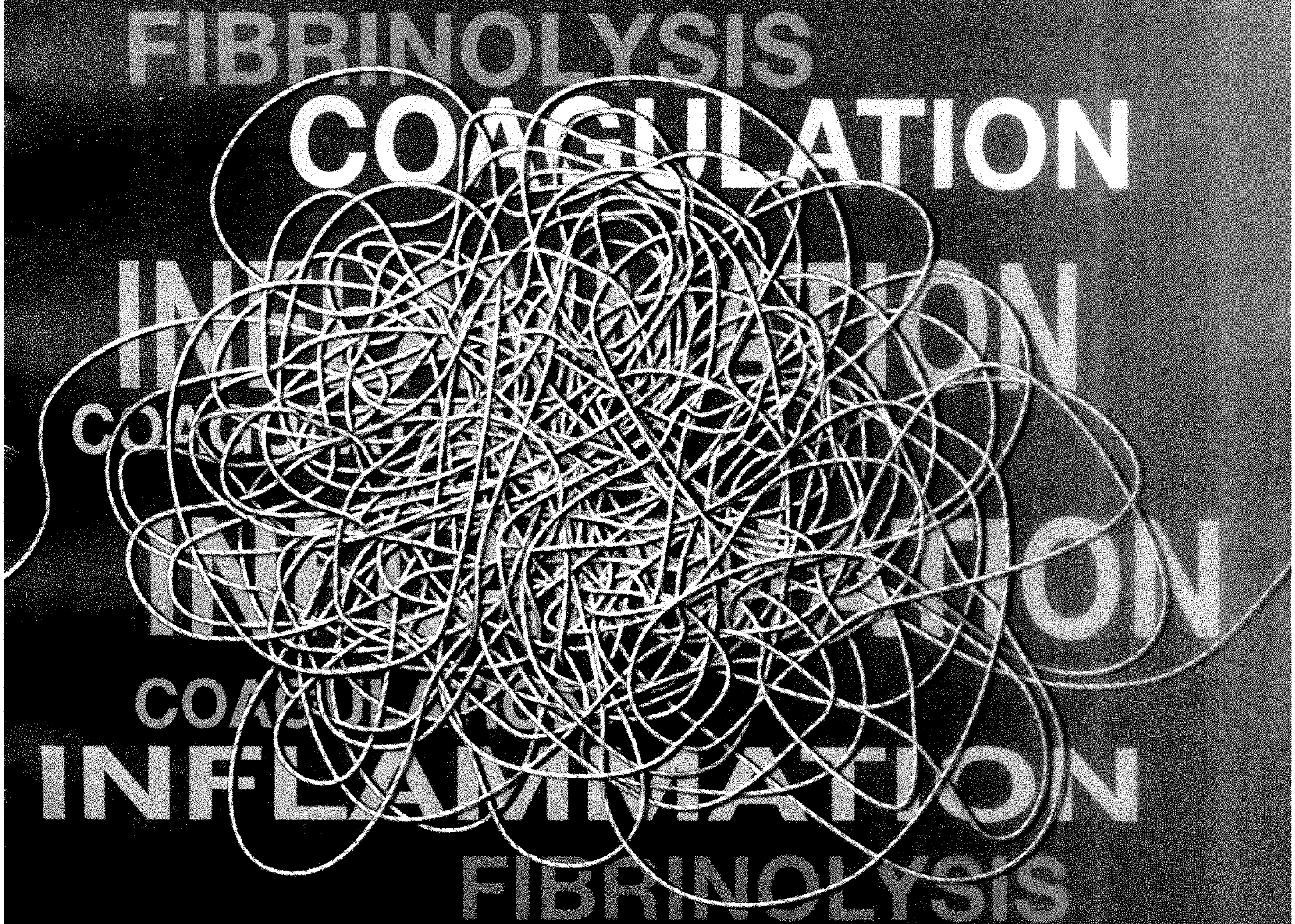
International Anaesthesia Research Society Annual Clinical and Scientific Congresses

78th Clinical and Scientific Congress of the International Anesthesia Research Society, Tampa Marriot Waterside Hotel, Tampa, Florida, March 27–31, 2004

79th Clinical and Scientific Congress of the International Anesthesia Research Society, Hilton Hawaiian Village, Honolulu, Hawaii, March 11–15, 2005

For information please contact: International Anesthesia Research Society, 2 Summit Park Drive, Suite 140, Cleveland, Ohio 44131–2553, USA. Tel: +1 16 642 1124; Fax: +1 216 642 1127; E-mail: iarshq@iars.org; Website: www.iars.org

Sepsis is difficult to unravel



Severe sepsis is a complex process. Even with the very best medical efforts, there is still significant mortality. There is now a much better understanding of how inflammation, coagulation and impaired fibrinolysis act together in severe sepsis.

Answers That Matter.

Austrian International Congress and Rudolf Kucher Forum

2nd International Danube Symposium

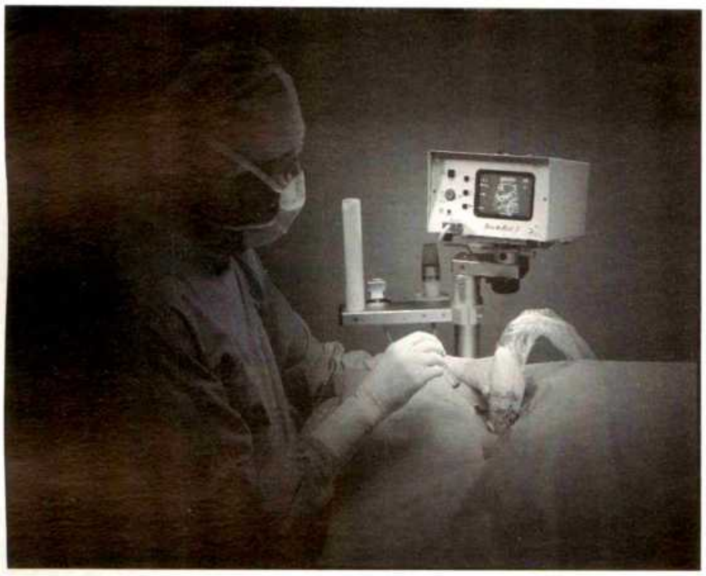
Anaesthesia & Intensive Care: Art or Science?
September 11–13, 2002 Vienna, Austria

Print copies of the meeting abstracts have been provided for Conference Delegates only. However, the abstracts will be available on-line to all BJA subscribers and are also freely available to all visitors to the following website from the date of the meeting (http://bja.oupjournals.org).

Print copies may be ordered from the Journals Subscriptions Department
(Email: jnls.cust.serve@oup.co.uk; Tel: +44 (0) 1865 353907; Fax: +44 (0) 1865 353485)
Price £27/US$42

SITE~RITE® 3

for real-time ultrasound-guided vascular access



NICE ONE!

Low Cost

Easy to use (See one, Do one, Teach one!)

See what you puncture

Significantly reduces risk of inadvertent arterial puncture, haematoma or pneumothorax

Choice of semi-permanent or disposable needle guides

Sole U.K. Distributor

Jade Medical
FREEPOST (RG2843)
Reading RG8 9ZZ
Tel:- 01491-874525
Fax:- 01491-874511
e-mail:-
sales@jade-medical.co.uk

"Site~Rite" is a registered trade mark of C.R. Bard, Inc., or an affiliate

Abbreviated version of the International summary of product characteristics

Therapeutic indications* Esmeron is indicated as an adjunct to general anesthesia to facilitate tracheal intubation during routine and rapid sequence induction,and to provide skeletal muscle relaxation during surgery. Esmeron is also indicated as an adjunct in the intensive care unit (ICU) to facilitate tracheal intubation and mechanical ventilation. Contra-indications: Former anaphylactic reactions to rocuronium or to the bromide ion. Special warnings and special precautions for use: Since Esmeron causes paralysis of the respiratory muscles, ventilatory support is mandatory for patients treated with this drug until adequate spontaneous respiration is restored. As with all neuromuscular blocking agents, it is important to anticipate intubation difficulties, particularly when used as part of a rapid sequence induction technique. Although very rare, severe anaphylactic reactions to neuromuscular blocking agents, including Esmeron, have been reported. These reactions have, in some cases, been fatal. Due to the possible severity of these reactions, one should always assume that they may occur and take the necessary precautions. Dose levels greater than 0.9 mg rocuronium bromide per kg body weight may increase the heart rate; this effect could counteract the bradycardia produced by other anesthetic agents or by vagal stimulation. In general, following long term use of muscle relaxants in the ICU, prolonged paralysis and/or skeletal muscle weakness has been noted. In order to help preclude possible prolongation of neuromuscular block and/or overdosage it is strongly recommended that neuromuscular transmission is monitored throughout the use of muscle relaxants. In addition, patients should receive adequate analgesia and sedation. Furthermore, muscle relaxants should be titrated to effect in the individual patients by or under supervision of experienced clinicians who are familiar with their actions and with appropriate neuromuscular monitoring techniques. Because Esmeron is always used with other agents and because the occurrence of malignant hyperthermia during anesthesia is possible, even in the absence of known triggering agents, clinicians should be familiar with early signs, confirmatory diagnosis and treatment of malignant hyperthermia prior to the start of any anesthesia. In animal studies, Esmeron was shown not to be a triggering factor for malignant hyperthermia. The following conditions may increase the effects of Esmeron: Hypokalemia (e.g. after severe vomiting, diarrhea and diuretic therapy), hypermagnesemia, hypocalcemia (after massive transfusions), hypoproteinemia, dehydration, acidosis, hypercapnia, cachexia. Severe electrolyte disturbances, altered blood pH or dehydration should therefore be corrected when possible.
* Therapeutic indications may vary from country to country.

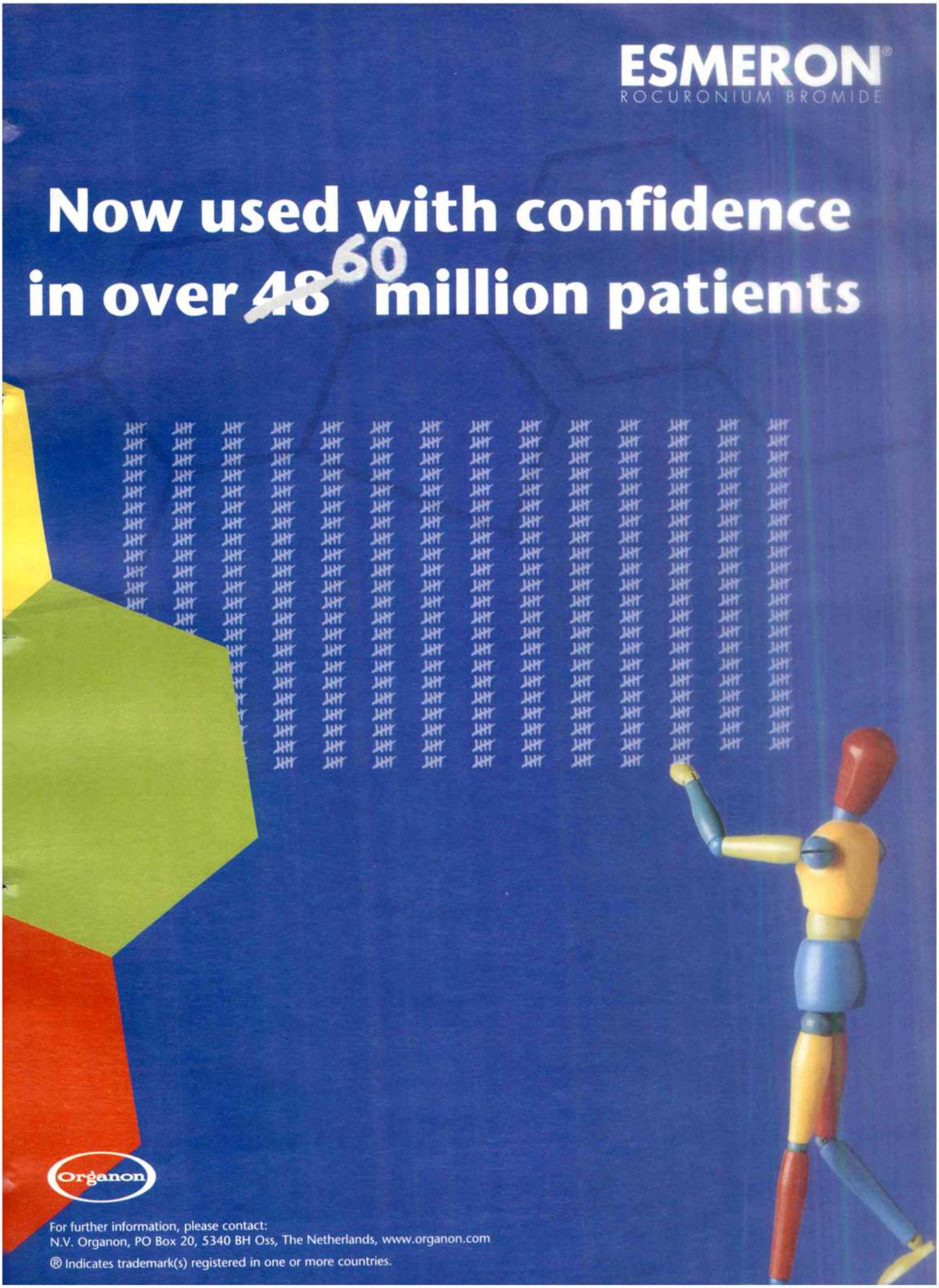
For full prescribing information see your local package insert.

December 1999

Organon

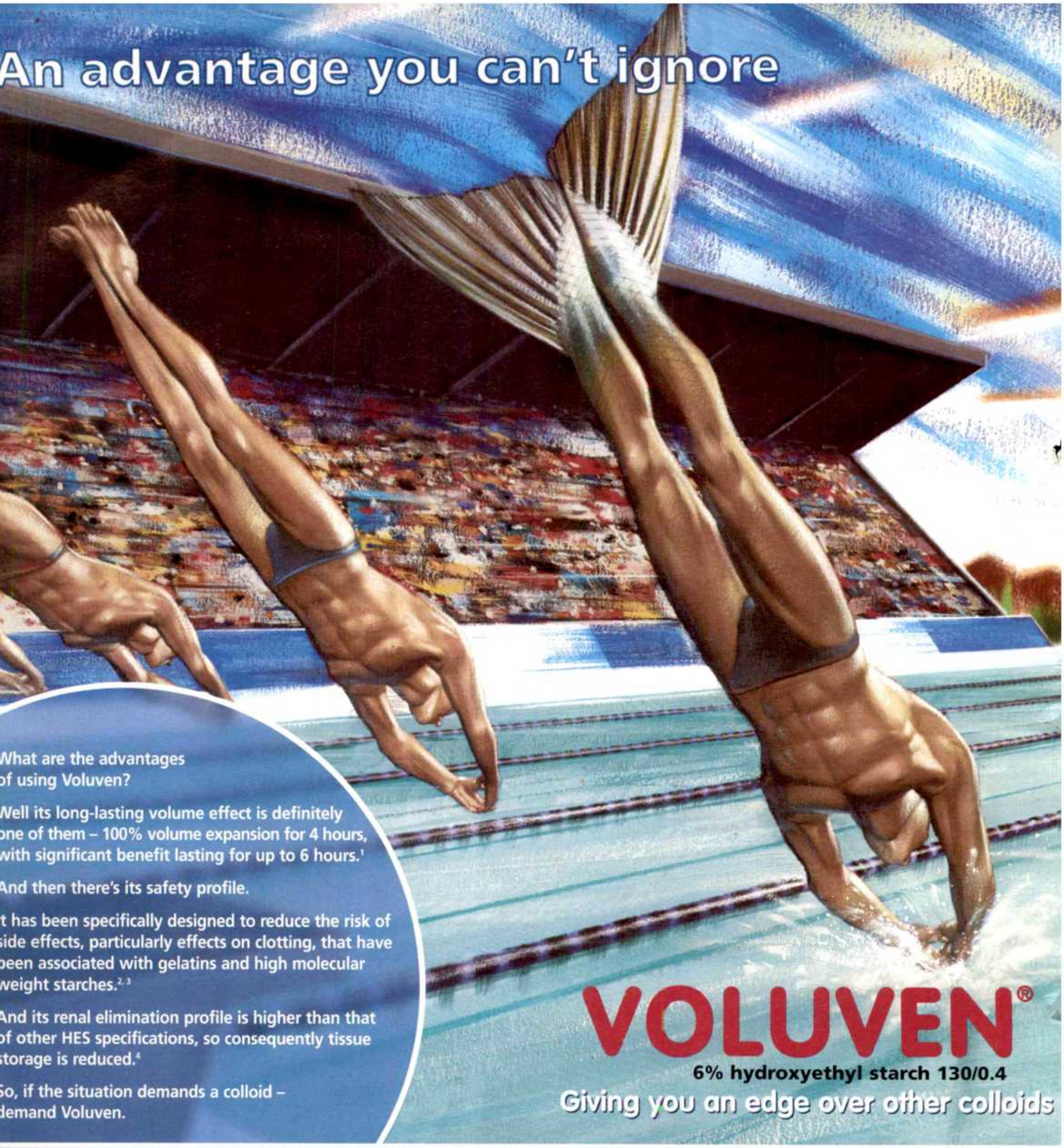
For further information, please contact:
N.V. Organon, PO Box 20, 5340 BH Oss, The Netherlands, www.organon.com

® Indicates trademark(s) registered in one or more countries.



For further information, please contact:
N.V. Organon, PO Box 20, 5340 BH Oss, The Netherlands, www.organon.com

® Indicates trademark(s) registered in one or more countries.



An advantage you can't ignore
VOLUVEN®
6% hydroxyethyl starch 130/0.4
Giving you an edge over other colloids

What are the advantages of using Voluven?

Well its long-lasting volume effect is definitely one of them – 100% volume expansion for 4 hours, with significant benefit lasting for up to 6 hours.[1]

And then there's its safety profile.

It has been specifically designed to reduce the risk of side effects, particularly effects on clotting, that have been associated with gelatins and high molecular weight starches.[2,3]

And its renal elimination profile is higher than that of other HES specifications, so consequently tissue storage is reduced.[4]

So, if the situation demands a colloid – demand Voluven.

Voluven Prescribing Information

Voluven® 6% solution for infusion (Hydroxyethyl Starch 130/0.4)

Presentation: 1000ml contains: Poly(O-2-hydroxyethyl) starch 60.00g (Molar substitution 0.38-0.45) (Mean molecular weight: 130,000) Sodium chloride 9.00g. **Indications:** Therapy and prophylaxis of hypovolaemia. **Posology and administration:** For continuous intravenous infusion. Daily dose and rate of infusion depend on blood loss, on the maintenance or restoration of haemodynamics and on the haemodilution (dilution effect). The maximum daily dose is 33ml/kg b.w./day. **Contra-indications:** Fluid overload, renal failure with oliguria or anuria, patients receiving dialysis treatment, intracranial bleeding, severe hypernatraemia or severe hyperchloraemia, known hypersensitivity to hydroxyethyl starches. **Precautions:** Avoid fluid overload caused by overdose. In severe dehydration, a crystalloid solution should first be given. Care must be taken in patients with severe liver disease or severe bleeding disorders. There are no data available on the use of Voluven® in children or pregnancy. **Side-effects:** Products containing hydroxyethyl starch may lead to anaphylactoid reactions in very rare cases. In the event of an intolerance reaction, the infusion should be discontinued and the appropriate emergency treatment initiated. The concentration of serum amylase can rise during administration and can interfere with the diagnosis of pancreatitis. Pruritus (itching) after prolonged administration of high dosages is a known undesirable effect of hydroxyethyl starches. At high dosages the dilution effects may result in a corresponding dilution of blood components such as coagulation factors and other plasma proteins and in a decrease of haematocrit. Disturbances of blood coagulation can occur depending on the dosage. **Basic NHS price:** UK – 500ml £12.50 per 500ml. Ireland – €15.24 per 500ml. **Authorisatin holder:** Fresenius Kabi Ltd, Melbury Park, Birchwood, Cheshire WA3 6FF. **Distributed in Ireland by:** Technopharm, Pharmapark, Chapelizod, Dublin 20. **MA number:** UK – PL 8828/0145, Ireland – PA 566/20/1. **Legal Category:** POM. **Date of Revision:** March 2002.

References

1. Waitzinger J, *et al.* Effect of a new HES specification (6% HES 130/0.4) on blood and plasma volumes after bleeding in 12 healthy male volunteers. Clin Drug Invest 1999; **17:** 119-125.
2. Ragaller MJR, *et al.* Volume replacement in critically ill patients with acute renal failure. J Am Soc Nephrol 2001; **12:** S33-S39.
3. Baron J-F. A new hydroxyethyl starch: HES 130/0.4, Voluven®. Transf Alt Transf Med 2000; **2:** 250.
4. Waitzinger J, *et al.* Pharmacokinetics and tolerability of a new hydroxyethyl starch (HES) specification [HES (130/0.4)] after a single dose infusion of 6% or 10% solution in healthy volunteers. Clin Drug Invest 1998; **16:** 151-160.

Freseniu
Kabi

For further information please contact Fresenius Kabi Medical Information on 01928 594311

BJA

"I would have everie man write what he knowes and no more."—Montaigne

BRITISH JOURNAL OF ANAESTHESIA

Volume 89, Number 4, October 2002

Editorial I

Intraperitoneal administration of analgesia: is this practice of any utility?

Local anaesthetic techniques are part of the multimodal approach to postoperative pain management.[1] This involves the use of opioids, non-steroidal anti-inflammatory drugs (NSAIDs)[2], paracetamol[3] and local anaesthetics.[4] The purpose of this editorial is to review whether or not instillation of local anaesthetics into the peritoneal cavity is a worthwhile modality in routine clinical practice during some intra-abdominal procedures.

Data from a nationwide survey in the UK of anaesthesia for gynaecological laparoscopy revealed that local anaesthetic solutions are administered commonly, particularly into the wound and the peritoneal cavity.[5] For this type of ambulatory surgery and anaesthesia, the main advantage of using local anaesthetics is that they do not have the adverse effects of opioids, which may delay recovery and discharge from hospital. These effects include postoperative nausea, sedation,[2] impairment of return of gastrointestinal motility, and pruritis. In addition, time to return of bowel function in the postoperative period may be reduced when the use of opioids is obviated by administering local anaesthetics.[6]

Although NSAIDs provide morphine-sparing effects[2], they do not appear, on their own, to provide sufficiently reliable postoperative analgesia for minimally invasive laparoscopic surgery.[7] In addition, they have the disadvantage that they may cause gastric irritation in addition to impairing platelet and renal function. In the perioperative period, many patients are at risk of these problems because of enforced starvation, dehydration and tissue trauma. Additional methods of analgesia are thus necessary.

Local anaesthetics have been administered into the peritoneal cavity during minimally invasive procedures, such as laparoscopic cholecystectomy and gynaecological laparoscopy for sterilization and diagnosis,[8] in addition to open abdominal procedures, such as total abdominal hysterectomy.[4 9 10] The rationale for this route of administration is that the peritoneum is exposed to block of visceral nociceptive conduction, thereby providing an additional mechanism of analgesia. However, absorption from the large peritoneal surface may also occur, and this may be a further mechanism of analgesia.

It has been shown after radical retropubic prostatectomy that i.v. lidocaine 1.5 mg kg^{-1} bolus and 2–3 mg min^{-1} infusion reduced morphine consumption and total pain scores significantly compared with placebo.[6] These data are supported by a clinical trial in which i.v. lidocaine produced a concentration-dependent reduction in pain scores when the plasma concentration exceeded 1.5 µg ml^{-1}.[11] In addition, it has been shown in rats that administration of systemic lidocaine may suppress peripheral ectopic impulse discharge[12] and inhibit central excitatory responses to glutamate.[13] With bupivacaine, the range of mean plasma concentration (0.92–1.14 µg ml^{-1}) after intraperitoneal instillation of plain bupivacaine 100–150 mg[14–16] is well below the toxic concentration of 3 µg ml^{-1}.[17] Similar systemic concentrations have produced neurological symptoms, such as paraesthesia, tingling and perioral numbness, in unanaesthetized volunteers during i.v. infusions of bupivacaine.[18 19] However, it remains unclear whether these concentrations produce a measurable postoperative analgesic effect.

Although laparoscopic cholecystectomy is a minimally invasive procedure, it is associated with intra-abdominal, incisional and shoulder pain after surgery.[20] Many clinical trials have been carried out to assess if intraperitoneal instillation of local anaesthetics to the gall bladder bed and right subdiaphragmatic space has produced any analgesic effect. Of 13 clinical trials in a systemic review[8] of intraperitoneal administration of bupivacaine 50–200 mg in volumes of 10–100 ml, significant reduction in overall pain occurred in seven trials but not in the other six. In addition, supplementary analgesic consumption was reduced significantly in five trials. This systematic review of bupivacaine concurs with a subsequent clinical trial in which intraperitoneal lidocaine 200 mg in 200 ml instilled under the right diaphragmatic surface increased time to first analgesia from 25 to 105 min after laparoscopic cholecystectomy.[21] Interestingly, in a recent study, an intraperitoneal combination of local anaesthetic and NSAID was shown to be more effective in reducing pain scores and opioid consumption than either placebo or intraperitoneal local anaesthetic with i.v. NSAID. Analgesic effects were greater in patients who had intraperitoneal lidocaine 200 mg with intraperitoneal tenoxicam 20 mg diluted to 200 ml compared with either placebo or intraperitoneal lidocaine 200 mg in 200 ml with i.v. tenoxicam 20 mg.[22] Thus it would appear that, for laparoscopic cholecystectomy,

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

intraperitoneal local anaesthetic solutions produce a modest analgesic effect which may not be adequate for routine analgesia.

Clinical trials of intraperitoneal instillation of local anaesthetics during gynaecological laparoscopy appear to demonstrate more effective analgesia, possibly because this operation is less traumatic than laparoscopic cholecystectomy.[8] In a systematic review of bupivacaine or etidocaine dripped onto the Fallopian tubes during laparoscopic sterilization under general anaesthesia, pain scores and supplementary analgesic consumption were reduced significantly for up to 2 h after surgery. Furthermore, intraperitoneal lidocaine, infiltrated into the mesosalpinx or into the Fallopian tubes, or coating Filshie slips, produced similar analgesic effects.[8] This has been confirmed in awake postpartum patients when intraperitoneal 0.5% lidocaine 80 ml reduced the need for supplementary fentanyl, ketamine and rescue general anaesthesia during tubal ligation.[23] In addition, intraperitoneal instillation of ropivacaine 150 mg during gynaecological laparoscopy produced a statistically significant 24 h morphine-sparing effect compared with placebo.[24]

The intraperitoneal cavity appears also to be an effective route for postoperative analgesia after administration of local anaesthetic in combination with an opioid. In a clinical trial of 100 patients undergoing laparoscopic tubal ligation, pain scores at rest and on movement were significantly lower in patients who had a combination of intraperitoneal meperidine 50 mg and intraperitoneal 0.125% bupivacaine 80 ml with epinephrine 1:200 000 compared with those who had a combination of i.m. meperidine 50 mg and intraperitoneal 0.125% bupivacaine 80 ml with epinephrine 1:200 000.[25]

In summary, it seems that intraperitoneal instillation of local anaesthetics is effective for gynaecological laparoscopy but may not be so for laparoscopic cholecystectomy.[8] Laparoscopic cholecystectomy is a longer procedure with greater tissue dissection than gynaecological laparoscopy. Recent evidence suggests that instillation of local anaesthetics both into the peritoneum and into the incision may be required after laparoscopic cholecystectomy. Instillation of ropivacaine 286 mg in 66 ml in this way during laparoscopic cholecystectomy produced lower pain scores and reduced morphine requirements compared with placebo.[26]

While intraperitoneal local anaesthetics have produced analgesic effects after gynaecological laparoscopy, they have not done so after total abdominal hysterectomy via a Pfannenstiel incision.[9] [10] Intraperitoneal instillation of either 0.5% bupivacaine 20 ml with epinephrine 1:200 000 diluted to 50 ml with normal saline or 2% lidocaine 20 ml with epinephrine 1:200 000 diluted to 50 ml with normal saline did not demonstrate any opioid-sparing effects compared with placebo.[10] It is likely that while intraperitoneal local anaesthetics may block visceral nociceptive conduction after minimally invasive surgery such as gynaecological laparoscopy, they do not block afferent nociceptive transmission from cutaneous sites. It appears that a combination of intraperitoneal and incisional administration of local anaesthetics is required after open abdominal procedures. Epinephrine 5 μg ml^{-1} with 0.25% bupivacaine 30 and 20 ml administered into the peritoneum and incision respectively produced morphine-sparing analgesia for 4 h after total abdominal hysterectomy via a Pfannenstiel incision.[4]

The difference in outcome of studies on intraperitoneal instillation of local anaesthetics may result from the type of surgery and the location, dose, type and timing of instillation. The failure in some studies to show an analgesic effect may result from rapid dilution of local anaesthetic in the peritoneal cavity.[27] It is not possible, however, to increase the dose of local anaesthetic without increasing the risk of systemic toxicity. Although potentially more toxic than lidocaine, bupivacaine has the advantage that it has a longer duration of action. However, in clinical trials the analgesic effects of bupivacaine have been short-lived. It has been shown in a mouse model that intraperitoneal bupivacaine in a liposomal formulation may prolong the duration of action and also reduce the possibility of systemic toxicity.[28] An alternative is levobupivacaine, the *S*(–) enantiomer of bupivacaine, the analgesic effects and duration of which are thought to be similar to those of racemic bupivacaine but with a reduced risk of systemic toxicity[29], thus allowing administration of a larger and more potent dose.

The intraperitoneal route of administration of local anaesthetic is simple: it does not involve additional central neural axial block and is particularly suited to the practice of ambulatory anaesthesia. However, for this route to be useful as a routine for pain management during all forms of minimally invasive surgery, it must not be limited by the dose of local anaesthetic. Thus the search goes on for newer, less toxic local anaesthetics that have a longer duration of action. It is hoped that this development may lead ultimately to improvements in convalescence and to a reduction in the risk of hospital readmission after minimally invasive surgery.

A. Ng
G. Smith
University Department of Anaesthesia, Critical Care & Pain Management
Leicester Royal Infirmary
Leicester LE1 5WW
UK

References

1 Michaloliakou C, Chung F, Sharma S. Preoperative multimodal analgesia facilitates recovery after ambulatory laparoscopic cholecystectomy. *Anesth Analg* 1996; **82**: 44–51
2 Ng A, Parker J, Toogood L, Cotton BR, Smith G. Does the opioid-sparing effect of rectal diclofenac following total

abdominal hysterectomy benefit the patient? *Br J Anaesth* 2002; **88**: 714–15

3 Montgomery JE, Sutherland CJ, Kestin IG, Sneyd JR. Morphine consumption in patients receiving rectal paracetamol and diclofenac alone and in combination. *Br J Anaesth* 1996; **77**: 445–7

4 Ng A, Swami A, Smith G, Davidson AC, Emembolu J. The analgesic effects of intraperitoneal and incisional bupivacaine with epinephrine following total abdominal hysterectomy. *Anesth Analg* 2002; **95**: 158–62

5 Simpson RB, Russell D. Anaesthesia for daycase gynaecological laparoscopy: a survey of clinical practice in the United Kingdom. *Anaesthesia* 1999; **54**: 51–85

6 Groudine SB, Fisher HAG, Kaufman RP, *et al.* Intravenous lidocaine speeds the return of bowel function, decreases postoperative pain and shortens hospital stay in patients undergoing radical retropubic prostatectomy. *Anesth Analg* 1998; **86**: 235–9

7 Alexander JI. Pain after laparoscopy. *Br J Anaesth* 1997; **79**: 369–78

8 Moiniche S, Jorgensen H, Wetterslev J, Berg J. Local anesthetic infiltration for postoperative pain relief after laparoscopy: a qualitative and quantitative systematic review of intraperitoneal, port-site infiltration and mesosalpinx block. *Anesth Analg* 2000; **90**: 899–912

9 Williamson KM, Cotton BR, Smith G. Intraperitoneal lignocaine for pain relief after total abdominal hysterectomy. *Br J Anaesth* 1997; **78**: 675–7

10 Ali PB, Cotton BR, Williamson KM, Smith G. Intraperitoneal bupivacaine or lidocaine does not provide analgesia after total abdominal hysterectomy. *Br J Anaesth* 1998; **80**: 245–7

11 Wallace MS, Dyck JB, Rossi SS, Yaksh TL. Computer-controlled lidocaine infusion for the evaluation of neuropathic pain after peripheral nerve injury. *Pain* 1996; **66**: 69–77

12 Devor M, Wall PD, Catalan N. Systemic lidocaine silences ectopic neuroma and DRG discharge without blocking nerve conduction *Pain* 1992; **48**: 261–8

13 Biella G, Sotgiu ML. Central effects of systemic lidocaine mediated by glycine spinal receptors: an iontophoretic study in the rat spinal cord. *Brain Res* 1993; **603**: 201–6

14 Narchi P, Benhamou D, Bouaziz H, Fernandez H, Mazoit JX. Serum concentrations of local anaesthetics following intraperitoneal administration during laparoscopy. *Eur J Clin Pharmacol* 1992; **42**. 223–5

15 Raetzell M, Maier C, Schroder D, Wulf H. Intraperitoneal application of bupivacaine during laparoscopic cholecystectomy—risk or benefit? *Anesth Analg* 1995; **81**: 967–72

16 Scheinin B, Kellokumpu I, Lindgren L, Haglund C, Rosenberg PH. Effect of intraperitoneal bupivacaine on pain after laparoscopic cholecystectomy. *Acta Anaesthesiol Scand* 1995; **39**: 195–8

17 Liu SS, Hodgson PS. Local anesthetics. In: Baresh PG, Cullen BF, Stoelting RK, eds. *Clinical Anesthesia*. Philadelphia: Lippincott Williams and Wilkins, 2001; 449–69

18 Knudsen K, Suurkula MB, Blomberg S, Sjovall J, Edvardsson Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers. *Br J Anaesth* 1997; **78**: 507–14

19 Scott DB, Lee A, Fagan D, Bowler GMR, Bloomfield P, Lundh R. Acute toxicity of ropivacaine compared with that of bupivacaine. *Anesth Analg* 1989; **69**: 563–9

20 Labille T, Mazoit JX, Paqueron X, Franco D, Benhamou D. The clinical efficacy and pharmacokinetics of intraperitoneal ropivacaine for laparoscopic cholecystectomy. *Anesth Analg* 2002; **94**: 100–5

21 Elhakim M, Elkott M, Ali NM, Tahoun HM. Intraperitoneal lidocaine for postoperative pain after laparoscopy. *Acta Anaesthesiol Scand* 2000; **44**: 280–4

22 Elhakim M, Amine H, Kamel S, Saad F. Effects of intraperitoneal lidocaine combined with intravenous or intraperitoneal tenoxicam on pain relief and bowel recovery after laparoscopic cholecystectomy. *Acta Anaesthesiol Scand* 2000, **44**: 929–33

23 Visalyaputra S, Lertakyamanee J, Pethpaisit N, Somprakit P, Parakkamodom S, Suwanapeum P. Intraperitoneal lidocaine decreases intraoperative pain during postpartum tubal ligation *Anesth Analg* 1999; **88**: 1077–88

24 Goldstein A, Grimault P, Henique A, Keller M, Fortin A, Darai E. Preventing postoperative pain by local anesthetic instillation after laparoscopic gynecologic surgery: a placebo-controlled comparison of bupivacaine and ropivacaine. *Anesth Analg* 2000; **91**: 403–7

25 Colbert S, Moran K, O'Hanlon D, *et al.* An assessment of the value of intraperitoneal meperidine for analgesia post-laparoscopic tubal ligation. *Anesth Analg* 2000; **91**: 667–70

26 Bisgaard T, Klarskov B, Kristiansen VB, *et al.* Multi-regional local anaesthetic infiltration during laparoscopic cholecystectomy in patients receiving prophylactic multi-modal analgesia: a randomized, double-blinded, placebo-controlled study. *Anesth Analg* 1999; **89**: 1017–24

27 Schulte-Steinbery H, Weninger E, Jokisch D, *et al* Intraperitoneal versus interpleural morphine or bupivacaine for pain after laparoscopic cholecystectomy. *Anesthesiology* 1995; **82**: 634–40

28 Grant GJ, Vermeulen K, Langerman L, Zakowski M, Turndorf H. Prolonged analgesia with liposomal bupivacaine in a mouse model. *Reg Anesth* 1994; **19**: 264–9

29 Foster RH, Markham A. Levobupivacaine. *Drugs* 2000; **59**: 551–79

Editorial II

Should we demand fresh red blood cells for perioperative and critically ill patients?

Blood transfusion has been practiced for almost 100 yr. This life-saving therapy was once regarded as 'one of the great advances in modern medicine'.[1] Times have changed; there are now very real concerns about the safety and efficacy of allogeneic stored blood. This shift in opinion has been precipitated by the greater awareness of transfusion-transmitted infections, most notably human immunodeficiency virus. More recently, clinical trials and animal experiments have raised doubts about the efficacy of transfusion.[2–4] A recent editorial in this journal stated that 'blood transfusion

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

(particularly with old blood) can paradoxically decrease microcirculatory oxygen delivery and contribute to tissue hypoxia'.[5]

Such statements need to be supported by sound evidence, as they lead us to believe that we should be demanding fresh blood for our patients. This is not a new idea, but such a change in practice could have crippling consequences for the UK's blood services, which face serious challenges to meet demand. To make blood available for essential patient needs when supplies are short, storage times need to increase rather than decrease.

Red blood cell (RBC) transfusion, like all therapies, carries risks. The risks of receiving a blood transfusion must be balanced against the risks of not receiving it. Some of the risks of transfusion are well documented and have been quantified, such as transfusion reactions and transmission of viral infections.[6 7] However, the importance of others, such as transfusion-related immunosuppression and the effect of storage on oxygen transport and delivery capabilities of RBCs after transfusion, are poorly understood. Even less is known about the potential for transmitting variant Creutzfeldt Jakob disease (vCJD) via blood transfusion. It is these unquantified risks that usually raise concerns among clinicians.

One of the problems with interpreting the evidence is that the properties of red cell concentrates vary greatly. Each donor unit contains a different amount of haemoglobin and even with national standards and guidelines, differences as a result of local variations in processing are inevitable.[8] In the UK, whole blood is collected into citrate-phosphate-dextrose anticoagulant and separated by centrifugation into red cell, platelet, and plasma components. The red cells are ultimately transferred into a pack containing an additive solution and stored at 4 (SD 2)°C. The currently used additive solution is a saline-adenine-glucose-mannitol (SAGM) solution, which, in the UK, is licensed for the storage of RBCs for up to 35 days. Other additive solutions are available, some of which, such as Adsol Preservation Solutions 1 and 3, are licensed for the storage of RBCs for up to 42 days. The collection and storage processes, and the regulations governing RBC storage, focus on maintaining cell integrity and viability; there are remarkably few studies looking at RBC function following transfusion.

Since 1999, all blood for transfusion in the UK has been leucodepleted at the point of initial processing. Leucodepletion was introduced in the hope that it would reduce the possible risk of vCJD transmission by blood transfusion. Secondary benefits of leucodepletion may be a reduction in the incidence of other adverse effects such as non-haemolytic transfusion reactions, cytomegalovirus transmission, alloimmunization, graft-*vs*-host disease, and transfusion-associated immunosuppression. There is also some evidence to suggest that white blood cells (WBCs) compromise the quality of red cell storage.[9–11] It is important to appreciate that most published studies of red cell transfusion used non-leucodepleted red cells rather than the product that we now use in the UK. This includes the TRICC study[4] that was discussed in the recent editorial in this journal.[5] The TRICC data suggest equivalent mortality with restrictive and liberal transfusion strategies, and provide compelling evidence that anaemia is well tolerated by most critically ill patients. The data showed a trend towards higher mortality in liberally transfused patients, particularly if young or less severely ill.

What evidence is there that the transfusion of stored blood has adverse clinical consequences?

There is substantial evidence from *in vitro* studies documenting the changes that RBCs undergo during storage (the so-called 'red cell storage lesion'). Red cell adenosine triphosphate decreases by 50% during storage and 2,3-diphosphoglycerate (2,3-DPG) is not maintained beyond 10 days. These changes increase the affinity of haemoglobin for oxygen and shift the oxygen dissociation curve leftwards. Red cells also undergo marked morphological changes during storage. These begin immediately after collection and consist largely of echinocytic change (the RBCs develop finger-like projections and adopt a spiky appearance). This shape change is initially reversible but with increasing duration of storage it becomes permanent as the finger-like projections bud off to form microvesicles (approximately 25% of membrane phospholipid is lost during 42 days of storage). The net effect of these morphological changes is a decrease in red cell deformability. Such observations make it reasonable to suggest that transfusing RBCs that are both 2,3-DPG depleted and poorly deformable could be ineffective and/or harmful, but there is scanty evidence to support this. Animal studies are problematic, because interspecies differences in RBC metabolism and structure mean that RBCs from different species behave differently during storage. For example, a much-quoted study found that 28-day-old rat blood failed to improve systemic oxygen consumption in rats in contrast to fresh rat blood.[3] Subsequent work has shown that rat RBCs deteriorate much more rapidly during storage than human RBCs and that after 28 days of storage, only 5% remain viable.[12]

Studies in humans attempting to determine the effect of blood transfusion on oxygen kinetics have not provided any clear answers. A recent review identified 14 studies evaluating the impact of RBC transfusion on oxygen kinetics.[13] Blood transfusion consistently increased oxygen delivery ($D\text{O}_2$), but oxygen consumption ($V\text{O}_2$) increased in only five of the studies. Several points warrant further consideration when interpreting these studies. First, most of the studies, including the five that reported an increase, calculated $V\text{O}_2$ which can introduce mathematical errors that erroneously link $D\text{O}_2$ and $V\text{O}_2$.[14] Secondly, the pre-transfusion haemoglobin concentration in these studies ranged from 8.3 to 11 g dl^{-1}, which is high compared with the TRICC study. Thirdly, the critical Do_2 threshold in critically ill patients is lower than previously thought, such that pathological oxygen supply dependency is not present in most clinically resuscitated critically ill patients with a haemoglobin concentration greater than 7–8 g dl^{-1}.[15] This questions the rationale for attempting to increase Do_2 by transfusion if haemoglobin concentration is above this level.

The data support a restrictive transfusion strategy but do not prove that the transfusion of stored RBCs has adverse effects or that they lack oxygen-carrying/delivering ability. An often-cited study of critically ill patients found, on retrospective analysis, an inverse association between the change in gastric intramucosal pH (pHi) and the age of the transfused blood.[2] Patients receiving non-leucodepleted blood that had been stored for more than 15 days had a decrease in pHi following RBC transfusion, which was interpreted as indicating worsening gastric oxygenation. A recent prospective, double blind, study randomized stable ICU patients to receive fresh (median storage age 2.3 days) or 'stored' (median storage age 28.2 days) leucodepleted red cell concentrates when pre-transfusion haemoglobin concentration was approximately 8 g dl^{-1}.[16] There was no change in Pco_2 gap, pHi or any measured oxygenation index following the transfusion of stored red cells.

There is very little evidence of an association between the storage age of transfused blood and patient outcome measures, such as morbidity and mortality. A retrospective study in patients with severe sepsis found that the duration of storage of transfused red cells was independently associated with ICU mortality, although the study was small (n=31).[17] A retrospective analysis of 268 patients who underwent coronary artery bypass graft surgery found a positive correlation between the duration of storage of the transfused red cells and the development of postoperative pneumonia.[18] In contrast, a subsequent study, from the same group, found no association between the transfusion of 'old' red cells and increased morbidity in cardiac patients (time to extubation, duration of ICU and hospital stay).[19] All of these studies were retrospective and they were unable to control the storage age of the transfused red cells, so that patients who received multiple transfusions often received blood of markedly different storage ages. In addition, all of these studies used non-leucodepleted red cells. To our knowledge, there are no published prospective, randomized studies comparing outcome when blood of different storage ages is administered. A recent randomized controlled trial that reduced allogeneic red cell transfusion in critically ill patients using erythropoietin found no difference in mortality between the two groups, although the study was not powered for this end-point.[20]

The best available evidence to date supports the use of a restrictive transfusion policy in most critically ill patients. Where transfusion is indicated, the clinical evidence to support a request for fresh RBCs is, however, poor. Interpreting the evidence is difficult because the introduction of universal leucodepletion has probably changed the properties of the current red cell product. One consequence of a move to requesting fresh blood for our patients would be to increase the risk of critical shortages and, therefore, to create new risks for patients whose management necessitates transfusion. Such a shift in practice would have to be based on sound evidence. This evidence has yet to be provided.

S. A. McLellan
T. S. Walsh
University Department of Anaesthetics
Critical Care and Pain Medicine
Royal Infirmary of Edinburgh
Edinburgh
UK

D. B. L. McClelland
Scottish National Blood Transfusion Service
Royal Infirmary of Edinburgh
Edinburgh
UK

References

1 Diamond, L. A history of blood transfusion. In· Wintrobe MM, eds. *Blood, Pure and Eloquent.* New York, NY: McGraw-Hill Book Company, 1980: 659–90

2 Marik PE, Sibbald WJ. Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. *JAMA* 1993; **269**: 3024–29

3 Fitzgerald RD, Martin CM, Dietz GE, *et al* Transfusing red blood cells stored in citrate phosphate dextrose adenine-1 for 28 days fails to improve tissue oxygenation in rats. *Crit Care Med* 1997; **25**: 726–32

4 Hebert PC, Wells G, Blajchman MA, *et al* A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med* 1999; **340**: 409–17

5 McCrossan L, Masterson G. Blood transfusion in critical illness *Br J Anaesth* 2002; **88**· 6–9

6 Love EM, Jones H, Williamson LM, *et al* Serious Hazards Of Transfusion Annual Report 1999/2000. ISBN 0 9532 789 3 X

7 Goodnough LT, Brecher M, Kanter MH, AuBuchon JP Transfusion medicine. First of two parts—blood transfusion. *N Engl J Med* 1999; **340**: 438–47

8 *Guidelines for the Blood Transfusion Services in the United Kingdom,* 5th Edn. The Stationery Office Ltd., 2001

9 Heaton WA, Holme S, Smith K, *et al* Effects of 3–5 log10 pre-storage leucocyte depletion on red cell storage and metabolism. *Br J Haematol* 1994; **87**: 363–8

10 Kristiansson M, Soop M, Shanwell A, Sundqvist KG. Prestorage versus bedside white blood cell filtration of red blood cell concentrates: effects on the content of cytokines and soluble tumor necrosis factor receptors *J Trauma* 1996; **40**· 379–83

11 Shanwell A, Kristiansson M, Remberger M, Ringden O. Generation of cytokines in red cell concentrates during storage is prevented by prestorage white cell reduction. *Transfusion* 1997; **37**: 678–84

12 d'Almeida MS, Jagger J, Duggan M, *et al.* A comparison of

biochemical and functional alterations of rat and human erythrocytes stored in CPDA-1 for 29 days: implications for animal models of transfusion. *Transfusion Med* 2000; **10**: 291–303

13 Hebert PC, Chin-Yee I. Clinical consequences of prolonged blood storage; should old red cell be transfused in critically ill patients? In: Vincent J-L, ed. *Yearbook of Intensive Care and Emergency Medicine*. Berlin, Heidelberg: Springer-Verlag, 2000; 494–506

14 Walsh TS, Lee A. Mathematical coupling in medical research: lessons from studies of oxygen kinetics. *Br J Anaesth* 1998; **81**: 118–20

15 Ronco JJ, Fenwick JC, Tweeddale MG, *et al.* Identification of the critical oxygen delivery for anaerobic metabolism in critically ill septic and nonseptic humans. *JAMA* 1993; **270**: 1724–30

16 Walsh TS, McArdle F, MacIver C, Maginnis M, McClelland DB. Age of stored red cells does not influence indices of oxygenation after transfusion to critically ill patients: randomised controlled trial. *Eur Soc Intensive Care Med* 2001; **27**: S247

17 Purdy FR, Tweeddale MG, Merrick PM. Association of mortality with age of blood transfused in septic ICU patients. *Can J Anaesth* 1997; **44**: 1256–61

18 Vamvakas EC, Carven JH. Transfusion and postoperative pneumonia in coronary artery bypass graft surgery: effect of the length of storage of transfused red cells. *Transfusion* 1999; **39**: 701–10

19 Vamvakas EC, Carven JH. Length of storage of transfused red cells and postoperative morbidity in patients undergoing coronary artery bypass graft surgery. *Transfusion* 2000; **40**: 101–9

20 Corwin HL, Gettinger A, Rodriguez RM, *et al.* Efficacy of recombinant human erythropoietin in the critically ill patient: a randomized, double-blind, placebo-controlled trial. *Crit Care Med* 1999; **27**: 2346–50

British Journal of Anaesthesia 89 (4). 541–5 (2002)

BJA

CLINICAL INVESTIGATIONS

Comparison of two techniques for measuring penetration of sodium chloride particles through breathing system filters

A. R. Wilkes[†]

Department of Anaesthetics and Intensive Care Medicine, University of Wales College of Medicine, Heath Park, Cardiff CF14 4XN, UK

Background. The filtration performance of breathing system filters can be determined by measuring the penetration of sodium chloride particles through the filter media.

Method. The penetration of sodium chloride particles through 12 breathing system filters was measured by two different techniques (using either forward light-scattering laser photometers or a neutral hydrogen flame photometer).

Results. The geometric means of the penetration values for the 12 filters varied from 0.0039% to 22.6% and from 0.0004% to 20.6% for the two techniques, respectively. For 10 of the 12 filters, with penetration values greater than 0.03%, the penetration values measured by, and the repeatability of, the two techniques were similar. The ratio of the penetration values measured by the two techniques (calculated from the mean difference in $\log_{10}$(penetration) between the two techniques for these 10 filters) was 0.93 (95% confidence interval 0.38 to 2.30). There is therefore only a small difference (at most a factor of about two either way) between the two techniques compared with the thousand-fold range in penetration values of the breathing system filters. For the remaining two filters, penetration values obtained using the flame photometer were less, and were close to or below the detection threshold of the laser photometer.

Conclusion. The neutral hydrogen flame photometer provides similar results to the forward light-scattering laser photometer technique.

Br J Anaesth 2002; **89:** 541–5

Keywords: equipment, heat and moisture exchange filters; measurement techniques, filtration

Accepted for publication; May 20, 2002

The British and European standard for breathing system filters, BS EN 13328-1, has been published recently.[1] Filtration performance is determined by measuring the penetration of sodium chloride particles through the filter [1] The particles specified in the standard are intended to have a size that is the most penetrating for the filter media. The aerosol of particles must have a size distribution with a count median diameter (CMD) in the range 0.055–0.095 µm and a geometric SD not exceeding 1.86, so that, assuming a lognormal distribution, 95% of the particles have a diameter between 0.022 and 0.26 µm. The total challenge must be in the range 0.1–0.3 mg. The terms used to define particle sizes are described in the Appendix.

An example of test equipment suitable for measuring filtration performance is given in the standard (Model AFT 8130, TSI Inc., St Paul, USA). The filtration performance of 33 breathing system filters has been measured using this equipment [2] That study showed that penetration differed between the two types of filter (pleated hydrophobic and electrostatic), and demonstrated that penetration was less for filters with larger surface areas.[2] However, it was not clear whether the penetration values obtained applied only to the particular test equipment used in the study.

[†] *Declaration of interest.* The author is funded by the Medical Devices Agency Manufacturers of some of the devices tested in this article have provided travel and subsistence expenses to visit their factories The Department of Anaesthetics and Intensive Care Medicine, University of Wales College of Medicine, undertakes commercial testing of some of these products

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Table 1 The twelve breathing system filters used during this study

Filter	Manufacturer	Address
Pleated hydrophobic		
BB22-15	Pall Medical Limited	Portsmouth, UK
BB25	Pall Medical Limited	Portsmouth, UK
HEPA filter/HME	Cory Bros Limited	London, UK
Sterivent Mini	DAR SpA	Mirandola, Italy
Thermovent HEPA	Portex Limited	Hythe, UK
Thermovent HEPA+	Portex Limited	Hythe, UK
Electrostatic		
Clear-Therm	Intersurgical Limited	Wokingham, UK
Filta-Therm	Intersurgical Limited	Wokingham, UK
Filtervent	Cory Bros Limited	London, UK
Humid-Vent Filter Compact	Louis Gibeck AB	Upplands-Vasby, Sweden
Humid-Vent Filter Light	Louis Gibeck AB	Upplands-Vasby, Sweden
Hygrobac S	DAR SpA	Mirandola, Italy

Other test equipment is available for measuring the penetration of sodium chloride particles through filter media. In particular, a test rig is available ('Moore's' Test Rig (CEN Bench Rig), SFP Services, Christchurch, UK) which was designed to measure the filtration performance of respiratory protective devices to the British and European standard, BS EN 143. This test rig may also be suitable for determining the filtration performance of breathing system filters, although the aerosol generators and the detection systems used to determine the penetration of sodium chloride particles are different in the two test rigs. New measurements on 12 filters by this alternative test rig were compared with previous measurements on the same 12 filters obtained using the TSI test equipment. This was carried out to determine whether the penetration of sodium chloride particles through filters measured by the two techniques is similar, provided the flow of air used is the same for both.

Methods

In the previous study,[2] the penetration of sodium chloride particles through five samples each of 33 different breathing system filters was measured using the example of suitable test equipment given in the European standard (Model AFT 8130, TSI Inc., St Paul, USA). This equipment generates an aerosol of sodium chloride particles with a size distribution complying with the standard, having a CMD of 0.07 μm, a geometric SD not exceeding 1.83, and with a mass concentration of 15 mg m^{-3}. The penetration values were obtained using a flow of air of 30 litre min^{-1} and each test lasted 26 s, so that the total challenge for each filter was 0.2 mg. The penetration of the particles through the filter was measured with two forward light-scattering photometers measuring the mass concentration of particles in the challenge and downstream of the filter. That test rig has a sensitivity of 0.001% penetration, and can measure penetration values up to 100%.

In the present study, the penetration of sodium chloride particles through five unused samples each of 12 of the different filters used in the previous study (Table 1) was measured using a second test rig ('Moore's' Test Rig (CEN Bench Rig), SFP Services, Christchurch, UK). The filters consisted of six pleated hydrophobic and six electrostatic filters, and covered the range of penetration values obtained during the previous study.[2] This test rig was designed to measure the performance of respiratory protective devices to the British and European standard, BS EN 143.[3] A Collison nebulizer generated sodium chloride particles from a 1% w/w sodium chloride solution. According to the manufacturer's specification, the diameter of the particles measured using the longest diagonal varied from 0.04 to 1.2 μm, with a mass median diameter of 0.6 μm. The mass median aerodynamic diameter is 0.4 μm with a mass concentration of particles of 13 mg m^{-3}. The penetration of the particles through the filter media was measured using a neutral hydrogen flame photometer. The intensity of the flame is proportional to the mass of sodium in the sample. The flame was viewed through a narrow-band interference filter with a half-peak bandwidth of 3 nm at 589.3 nm. Neutral density filters were used to prevent the light transmission flooding the photomultiplier. The minimum detectable penetration was 0.000005%. Penetration was again measured with a flow of 30 litre min^{-1} of air passing through the filter under test. The output from the photomultiplier was displayed on an analog meter, and the reading was recorded within 30 s of initiating flow through the filter. The penetration (%) was calculated from tables provided by the manufacturer (SFP Services), taking into account the neutral density filter that was used.

Statistical analysis

The two methods of measurement were compared using the method described by Bland and Altman.[4] A comparison of the two methods can be made, provided the repeatability of the methods is similar. The repeatability of a method is usually assessed by calculating the variance of repeated measurements made on a single subject. However, it is known that challenging a filter with sodium chloride particles affects subsequent measurements of penetration.[5] Therefore, in this study, the variance of each technique was calculated from the results of one challenge on each of five samples of each different filter tested.

Log_{10}(penetration) values were used for analysis because, with the large range in penetration values obtained, this led to more consistent variances over the range of penetration. The variances of the log_{10}(penetration) values of each filter measured by each of the two techniques were calculated. The variances of the log_{10}(penetration) values from the two techniques of measurement were compared using the paired *t*-test (StatView 5, SAS Institute Inc., SAS Campus Drive, Cary, USA).[6] The null hypothesis was that there is no difference between the variances for the two techniques. If the hypothesis was correct, the comparison of the two techniques could then be made.

The mean $\log_{10}$(penetration) for each filter measured by each technique was calculated. The difference between the two means for each filter was plotted against the average of the two (Fig. 1). The mean difference (*d*) and the standard deviation (s_D) of the differences between the two techniques were calculated. When repeated measurements are made, the limits of agreement are wider than those given by $d \pm 1.96 s_D$, because the averaging of the repeated measurements has removed some of the random error associated with each individual measurement.[4] The corrected standard deviation of the differences, s_C, is $\sqrt{(s_D^2 + \frac{1}{4}s_A^2 + \frac{1}{4}s_B^2)}$, where s_A and s_B are the standard deviations for the two different methods A and B.[4] s_A and s_B were taken to be the square root of the mean of the variances of $\log_{10}$(penetration) for each method. The limits of agreement are then $d \pm 1.96 s_C$. This gives the limits of agreement for a pair of single measurements on a given filter by the two techniques.

If the variances of the two techniques are similar, the variances can be pooled and an estimate can be calculated of the error associated with the difference between, and the mean of, the $\log_{10}$(penetration) values for each filter. The pooled standard deviation, s_P, is $\sqrt{((s_A^2 + s_B^2)/2)}$, and the standard error of the mean of any five measurements, SE, is $s_P/\sqrt{5}$. The errors associated with the difference between, and the mean of, the values for each filter from the two techniques are $\text{SE}\sqrt{2}$ and $\text{SE}/\sqrt{2}$, respectively. The 95% confidence intervals (CI) for the difference and the mean for each filter are then $\pm t\text{SE}\sqrt{2}$ and $\pm t\text{SE}/\sqrt{2}$, respectively.

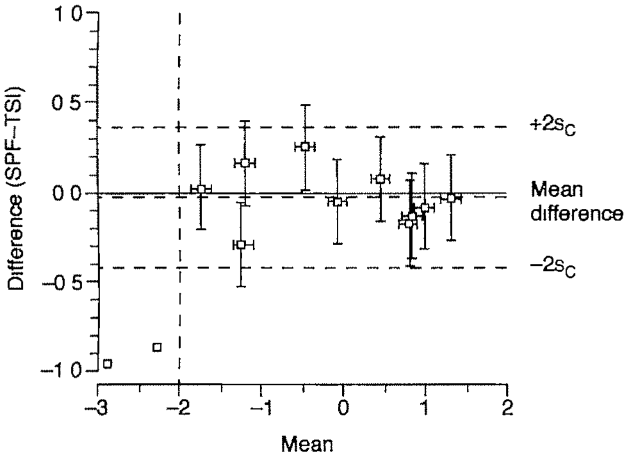


Fig. 1 Difference against mean for the mean $\log_{10}$(penetration) values obtained from the two techniques for the 12 filters. The limits of agreement were obtained by omitting from the calculations two filters with mean $\log_{10}$(penetration) values less than –2 (equivalent to a penetration of 0.01%, or an efficiency of 99.99%). The 95% CI for the difference and mean for each filter are shown

Results

The geometric means of the penetration values for the 12 filters varied from 0.0004% to 20.6% for the SFP test rig, and from 0.004% to 22.6% for the TSI test rig. The pleated hydrophobic filters have smaller penetration values than the electrostatic filters (Table 2). The penetration of one sample of one filter was 0% on the TSI rig. A value of 0.0005% (half the limit of sensitivity of 0.001% for the TSI rig) was used when taking logs in the analysis. The highest penetration measured was 27.3%.

The means of the variances of the $\log_{10}$(penetration) values obtained from the SFP and TSI test rigs were 0.020 and 0.062, respectively. The paired *t*-test did not demonstrate a significant difference between the pairs of variances of the $\log_{10}$(penetration) values for each filter obtained by the two techniques (mean difference was –0.041, 95% CI –0.099 to 0.016, $P=0.14$). Therefore, the results are consistent with the hypothesis that the variances (and hence the repeatabilities) of the two techniques are the same.

Table 2 Geometric mean penetration values through the twelve breathing system filters for each technique (SFP and TSI), with values of variance [$\log_{10}$(penetration)] for each filter

Filter	Penetration (%) (geomean, *n*=5)		Variance [$\log_{10}$(penetration)]		Difference
	SFP	TSI	SFP	TSI	
Pleated hydrophobic					
BB22-15	0.020	0.019	0.0158	0.0092	–0.0066
BB25	0.082	0.056	0.0056	0.0014	–0.0042
HEPA filter/HME	0.044	0.087	0.0675	0.3290	0.2615
Sterivent Mini	0.859	0.973	0.0026	0.0032	0.0006
Thermovent HEPA	0.0021	0.015	0.0113	0.0394	0.0280
Thermovent HEPA+	0.0004	0.0039	0.0953	0.2962	0.2009
Electrostatic					
Clear-Therm	3.36	2.85	0.0033	0.0039	0.0006
Filta-Therm	0.490	0.275	0.0041	0.0034	–0.0006
Filtervent	5.41	8.17	0.0258	0.0151	–0.0107
Humid-Vent Filter Compact	6.18	8.54	0.0048	0.0310	0.0263
Humid-Vent Filter Light	20.6	22.6	0.0040	0.0039	–0.0001
Hygrobac S	9.27	11.44	0.0046	0.0056	0.0010
Mean			0.0204	0.0618	0.0414
Mean without Thermovent HEPA and HEPA+			0.0138	0.0406	0.0268

Table 3 $\log_{10}$(penetration) values through the twelve breathing system filters for each technique (SFP and TSI), with mean and difference for each filter

Filter	$\log_{10}$(penetration) (%) (mean, n=5)		Mean	Difference
	SFP	TSI		
Pleated hydrophobic				
BB22-15	−1.697	−1.720	−1.709	0.023
BB25	−1.088	−1.252	−1.170	0.163
HEPA filter/HME	−1.357	−1.061	−1.209	−0.295
Sterivent Mini	−0.066	−0.012	−0.039	−0.054
Thermovent HEPA	−2.690	−1.837	−2.263	−0.853
Thermovent HEPA+	−3.370	−2.409	−2.890	−0.961
Electrostatic				
Clear-Therm	0.526	0.455	0.491	0.070
Filta-Therm	−0.310	−0.560	−0.435	0.250
Filtervent	0.733	0.912	0.823	−0.179
Humid-Vent Filter Compact	0.791	0.931	0.861	−0.140
Humid-Vent Filter Light	1.314	1.355	1.335	−0.040
Hygrobac S	0.967	1.053	1.013	−0.091
Mean				−0.176
Mean without Thermovent HEPA and HEPA+				−0.0294

The plot of difference against mean of $\log_{10}$(penetration) for the two techniques showed that there were two obvious outliers, with the penetration values measured by the SFP test rig less than those measured by the TSI equipment (Fig. 1). All 20 measurements of penetration for these two filters by the two techniques were less than 0.03%, giving a filtration efficiency of greater than 99.97% for both filters. A filter with a filtration efficiency greater than 99.97% is the highest category according to the National Institute for Occupational Safety and Health (NIOSH) standard for respiratory protective devices.[7] Both techniques placed the two filters into this category, but the difference between the techniques for these two filters skewed the analysis of the comparison. The penetration values were also close to the limit of sensitivity of the TSI test equipment (0.001%). These filters were therefore removed from the following analysis, and the calculations on the difference between the two techniques were made on the results from the remaining 10 filters.

The two methods of measurement were compared using the method reported by Bland and Altman,[4] described briefly above. The mean difference in $\log_{10}$(penetration) between the two techniques was −0.0294 (Table 3). The standard deviation of the differences between the means of $\log_{10}$(penetration) values measured by the two techniques (s_D) was 0.162. The standard deviation from the SFP rig, s_A, was 0.117 and from the TSI rig, s_B, was 0.201, giving the corrected standard deviation from which to calculate the limits of agreement, s_C, as 0.20. The limits of agreement were therefore −0.42 and 0.36. The antilog of the mean difference was 0.93, and antilogs of the limits of agreement gave 0.38 and 2.30. Therefore, on average, the SFP technique gave penetration values 0.93 times that of the TSI technique, although the ratio between a pair of single measurements by the two methods on any given filter may be as little as 0.4 or as much as 2.3.

The pooled SD was 0.165, giving an SE of 0.074 from which to calculate the 95% CI associated with the difference between and the mean of the $\log_{10}$(penetration) values from the two techniques.

Discussion

The penetration values measured on 10 filters by the two techniques showed good agreement over the range of penetration values from 0.03% to about 25%, corresponding to filtration efficiencies of 99.97% to 75%. Although the penetration values measured by the SFP technique may be from 0.4 to 2.3 times that of the TSI technique, this is a small difference compared with the thousand-fold range from the worst to the best filter performance. The TSI equipment is given in the standard for breathing system filters as an example of test equipment suited to measurement of penetration values. From the present study, the SFP test equipment can also be used, as it will provide similar results, and will also provide greater sensitivity when measuring the penetration of sodium chloride particles through filters with low penetration values.

The TSI equipment measures the light scattered by any particle in the air. Particles released by the breathing system filter itself could be counted as 'penetration' particles. Hygroscopic salts added to the heat and moisture exchanger layer in the filter may be released during the test, causing an apparent, but incorrect, increase in the penetration value. However, the flame photometer only measures particles containing sodium, and, as there was good agreement between the two techniques, the error associated with the release of particles from the filters must be small.

The penetration of particles though a filter depends on, amongst other factors, the size of the particles in the challenge. The size distribution of particles used to challenge the filter is specified in the standard to have a

CMD of 0.075 (SD 0.020) μm and a geometric SD not exceeding 1.86. Particles with different diameters penetrate through filter media with varying efficiencies. Particles that are the most penetrating have a diameter in the range 0.05–0.5 μm.[8] The most penetrating particle size depends on the face velocity (volume flow rate of air per unit area of filter media), the diameter of the fibre and the packing density of the fibres.[8] Therefore, the size of the most penetrating particle will vary for different filters.

The TSI equipment complies with the requirement of the standard, generating an aerosol of sodium chloride particles with a CMD of 0.07 μm and a geometric SD not exceeding 1.83. SFP claims that its test equipment generates an aerosol of sodium chloride particles with a range of particle size of 0.04–1.2 μm when measured using the longest diagonal, and a mass median aerodynamic diameter of 0.4 μm. However, an aerosol of particles with a CMD of 0.07 μm and a geometric SD of 1.83 has a mass median aerodynamic diameter of 0.34 μm (see Appendix). Therefore, from theory, the two techniques should provide nearly the same results if the total challenge is similar (product of mass concentration and time). In the present study this was so, over the range of penetration values 0.03–25%.

Acknowledgements

The technical work for this study was carried out at Air Safety Limited, Morecambe, UK. I would like to thank the staff at Air Safety for the generous loan of the test apparatus, and for their technical assistance during this study

Appendix

Particle size terminology

Count median diameter (CMD)

The size of aerosol particles can be stated in a number of different ways. The physical diameter is given for particles in the standard for breathing system filters.[1] Assuming that the distribution of the particle sizes can be described by the lognormal distribution, the size distribution is stated in terms of the CMD and the geometric SD (σ_g). The CMD is the diameter for which 50% of the particles have a diameter larger and 50% have a diameter smaller than this value. σ_g is given by:

$$\ln\sigma_g = \{\Sigma n_i (\ln d_i - \ln d_g)^2/(N-1)\}^{0.5}$$

where d_i is the diameter of the ith particle, d_g is the geometric mean diameter (which equals CMD for a lognormal distribution), n_i is the number of particles in the ith group, and N is the total number of particles. For the lognormal distribution, 95% of the particles lie between $\text{CMD} \div \sigma_g^2$ and $\text{CMD} \times \sigma_g^2$.

The mass median diameter (MMD)

The MMD is the diameter for which 50% of the total mass of the particles is contributed by particles with a diameter larger and 50% by particles with a diameter smaller than this value. The MMD can be obtained from the CMD from the following Hatch–Choate equation.[8]

$$\text{MMD} = \text{CMD} \exp 3 (\ln\sigma_g)^2$$

The aerodynamic diameter

An alternative approach is to quote the diameter of the particle in aerodynamic terms, that is, an equivalent diameter so that, regardless of the density or shape of the particle, all particles with the same aerodynamic diameter will behave in the same way, for example, by having the same terminal velocity under gravity in air.

The aerodynamic diameter, d_a, of a single spherical sodium chloride particle with a physical diameter, d_p, is given by:[8]

$$d_a = d_p\{C_c(d_p) / C_c(d_a)\}^{0.5} \{\rho_p / \rho_0\}^{0.5} \qquad (1)$$

where ρ_0 is the standard density (1000 kg m^{-3}), ρ_p is the density of the particle (2165 kg m^{-3} for sodium chloride) and C_c is the Cunningham (slip) correction factor, a factor that has to be included when the size of the particle is close to the mean free path of the air molecules. C_c is given by:[8]

$$C_c = 1 + (\lambda / d)\{2.34 + 1.05 \exp(-0.39\, d/\lambda)\}$$

where d is the diameter of the particle (μm), and λ is the mean free path of the air molecules, which is 0.0665 μm at 20°C and 101.3 kPa.

Since the aerodynamic diameter, d_a, occurs on both sides of equation (1), it needs to be calculated iteratively. A shape factor has to be included for particles that are not spherical.[8]

Example

If CMD=0.07 μm and σ_g=1.83, then 95% of the particles lie between 0.021 and 0.23 μm. The equivalent MMD=0.21 μm and the mass median aerodynamic diameter is 0.34 μm.

References

1 British Standards Institution. Breathing system filters for anaesthetic and respiratory use – Part 1: salt test method to assess filtration performance (BS EN 13328-1:2001). Milton Keynes, UK: British Standards Institution, 2001

2 Wilkes AR. Measuring the filtration performance of breathing system filters using sodium chloride particles. *Anaesthesia* 2002; **57**: 162–8

3 British Standards Institution. Specification for particle filters used in respiratory protective devices (BS EN 143:1991). Milton Keynes, UK: British Standards Institution, 1991

4 Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; **i**: 307–10

5 Wilkes AR. Factors affecting the filtration performance of breathing system filters. *Br J Anaesth* 2000; **84**: 280P

6 Bland JM Comparing within-subject variances in a study to compare two methods of measurement. http://www.sghms.ac.uk/phs/staff/jmb/jmb.htm, 22 April, 2001

7 National Institute for Occupational Safety and Health (NIOSH). Respiratory Protective Devices. Code of Federal Regulations, Title 42, Part 84. Morgantown, West Virginia, USA: National Institute for Occupational Safety and Health, 1995

8 Hinds WC. *Aerosol Technology. Properties, Behavior, and Measurement of Airborne Particles*, 2nd Edn. New York: John Wiley and Sons, 1999

British Journal of Anaesthesia 89 (4): 546–50 (2002)

Xenon has no effect on cytokine balance and adhesion molecule expression within an isolated cardiopulmonary bypass system[†‡]

A. Bedi[1 2*], W. T. McBride[1 2], M. A. Armstrong[3], J. M. Murray[2] and J. P. H. Fee[2]

[1]Anaesthesia and Intensive Care Medicine, The Royal Group of Hospitals Trust, Grosvenor Road, Belfast BT12 6BA, [2]Department of Anaesthetics and Intensive Care Medicine and [3]Department of Microbiology and Immunobiology, Queen's University of Belfast, Whitla Medical Building, 97 Lisburn Road, Belfast BT9 7BL, UK

**Corresponding author: Department of Anaesthetics and Intensive Care Medicine, Whitla Medical Building, 97 Lisburn Road, Belfast BT9 7BL, UK*

Background. Although almost inert chemically, xenon is not unreactive biologically. It interacts with receptors involved in the expression of cytokines and adhesion molecules. The effect of xenon on the immune function in whole blood has not been studied.

Methods. We examined the effects of 70% xenon in oxygen on cytokine balance and expression of adhesion molecules in an isolated cardiopulmonary bypass (CPB) system, which simulates an evolving inflammatory response. Whole blood from 10 healthy male volunteers was circulated in a CBP system supplied with either 70% xenon in oxygen, or oxygen-enriched air – F_{O_2}=0.3 (control). We took samples of blood after 30, 60 and 90 min of simulated CBP. We measured interleukin (IL)-1β, tumour necrosis factor (TNF)α, IL-8, IL-10, IL-1ra and TNF-sr-2 levels, and the expression of HLA-DR and the adhesion molecules L-selectin, CD18 and CD11b on monocytes, granulocytes and lymphocytes.

Results. IL-8 concentrations were increased significantly, TNF-sr-2 concentrations decreased significantly and IL-10 levels decreased during bypass. There were no significant differences between the groups for any measured variable.

Conclusion. In an isolated CPB system, xenon and oxygen-enriched air had similar effects on cytokine production and expression of adhesion molecules.

Br J Anaesth 2002; **88**: 546–50

Keywords: anaesthetic gases, xenon; immune response; polypeptides, cytokines, adhesion molecules; surgery, cardiopulmonary bypass

Accepted for publication: April 28, 2002

Xenon is an inert gas with potent anaesthetic and analgesic properties which could replace nitrous oxide. It acts on the *N*-methyl-D-aspartate (NMDA) receptor[1] and interferes with intracellular calcium homeostasis.[2 3] Because both these mechanisms are involved in cytokine and adhesion molecule expression, it is possible that xenon could modify the normal human immune response to inflammation.

Extracorporeal cardiopulmonary bypass (CPB) stimulates an intense, progressive inflammatory response which includes complement activation, increased adhesion molecule expression and an increase in the plasma concentrations of pro-inflammatory cytokines. We have used this isolated CBP model to study the effects of various anaesthetic medications on the human immune system.[4]

Because the effects of xenon on immune function are not known, we used the same CPB system to compare the effects of 70% xenon in 30% oxygen with oxygen-enriched air (F_{O_2}=0.3) on the production of L-selectin, HLA-DR, CD18, CD11b, interleukin (IL)-1β, tumour necrosis factor (TNF)α, IL-8, IL-10, IL-1ra and TNF-sr-2 during 90 min of simulated CPB.

[†] *Declaration of interest.* We are grateful to Polystan UK who provided the cardiopulmonary bypass circuits for this study. This study was supported by a grant from BOC gases (UK) for the ELISA assays and supply of xenon Dr Bedi was supported by a Research Fellowship from the Association of Anaesthetists of Great Britain and Ireland (1998–2000)

[‡] This work was presented as an abstract to the Anaesthetic Research Society.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Methods

After obtaining local research ethics committee approval and written informed consent, 10 healthy male volunteers, who were not receiving any medication and had refrained from alcohol and caffeine for 24 h, each donated two 250-ml samples of blood into standard blood donation bags containing SAG-M anticoagulant. Heparin (1000 IU) was added to each bag. The donated blood was immediately circulated in one of two identical CPB circuits each primed with 270 ml Hartmann's solution. A trained perfusionist commenced simulated bypass at 37°C. Flow through the bypass apparatus was maintained at 2.5 litre min^{-1}. The membrane oxygenator of each bypass apparatus was then supplied with either 70% xenon in 30% oxygen, or oxygen-enriched air ($F\text{O}_2$=0.3). Each membrane oxygenator was also supplied with carbon dioxide using a calibrated flowmeter, as required, to maintain the partial pressure of carbon dioxide within the blood between 4 and 6 kPa. The fractions of gas delivered to each membrane oxygenator were monitored using a Capnomac Ultima (Datex Engstrom, Helsinki, Finland) and the xenon concentration was monitored using a thermal conductivity meter calibrated for the measurement of xenon in oxygen (Bedfont Scientific, Rochester, UK).

A 10-ml sample of blood was taken from each bag after donation (time 0) and from each membrane oxygenator at 30, 60 and 90 min. Samples were processed immediately. Four 0.1-ml aliquots of whole blood were stained using monoclonal antibodies for CD18, CD11b (Flow Cytometry Primary Antibodies and Conjugates, Dako Ltd, Denmark), L-selectin, HLA-DR and mouse IgG [control] (Becton, Dickinson and Company, NJ, USA). The whole blood was then lysed to remove the red cells, thus permitting the expression of surface markers on white blood cells to be determined using flow cytometry. Quantification of the adhesion molecules was carried out immediately after acquisition and processing of the samples, by a laboratory technician skilled in this field. Flow cytometric analyses were performed on an EPICS ELITE instrument (Coulter Electronics Ltd, Luton, UK). This instrument was calibrated before each series of analyses by a technician trained in this method, using Immno-Check alignment fluorospheres (Coulter Corporation, Hialah, FL, USA). Two thousand cells were analysed and displayed as dot histograms for each assay. Following subtraction of the background staining from the control samples, the percent positivity and mean channel fluorescence (MCF) intensity of the respective cell populations was determined.

At the same time, the second 250-ml sample of blood was centrifuged to separate the plasma, which was aliquoted and stored at –70°C for future analysis of the pro-inflammatory cytokines IL1-β, TNFα, IL-8 and the anti-inflammatory cytokines IL-10, IL-1ra and TNF-sr-2. A commercially available enzyme-linked immunoabsorbent assay (ELISA) (Quantikine™, R&D Systems, Abingdon, UK) was used for all cytokine assays.

Statistical analysis

The normality of the data was inspected and subsequent statistical analyses were performed using GraphPad Prism™

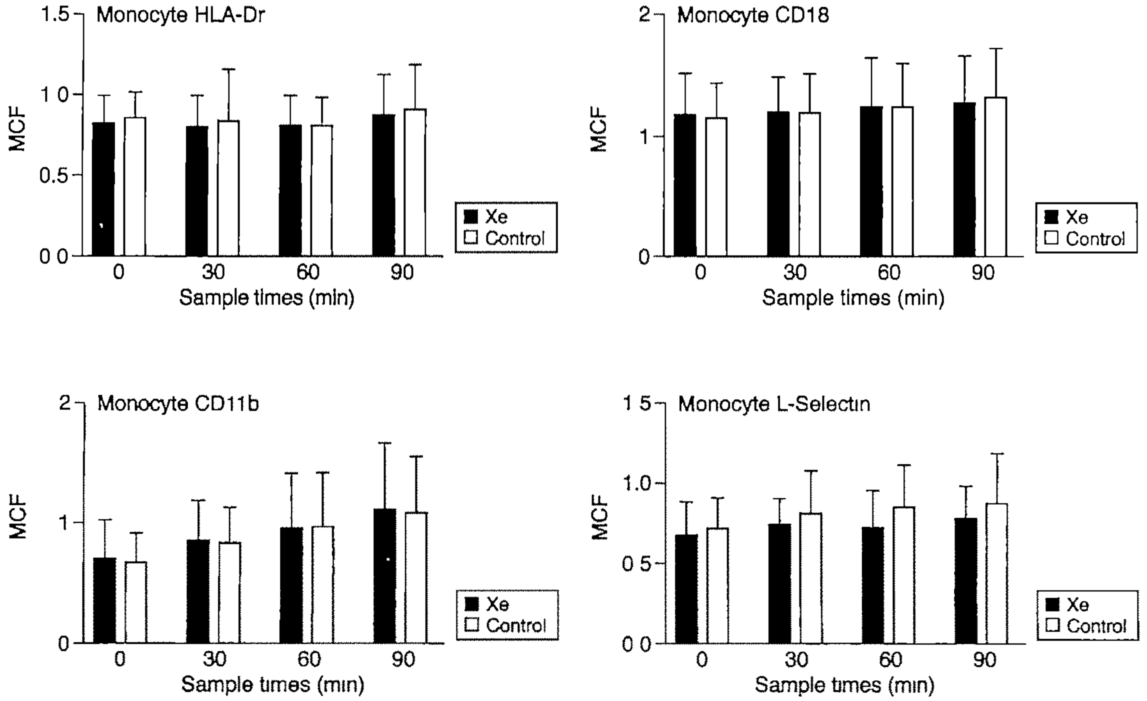


Fig 1 The mean channel fluorescence (MCF), expressed as linear units, of monocyte HLA-Dr, CD18, CD11b and L-selectin in donor blood at baseline (time 0) and after 30, 60 and 90 min of isolated CPB with xenon in oxygen, and with oxygen-enriched air (control) The error bars represent 1 SD

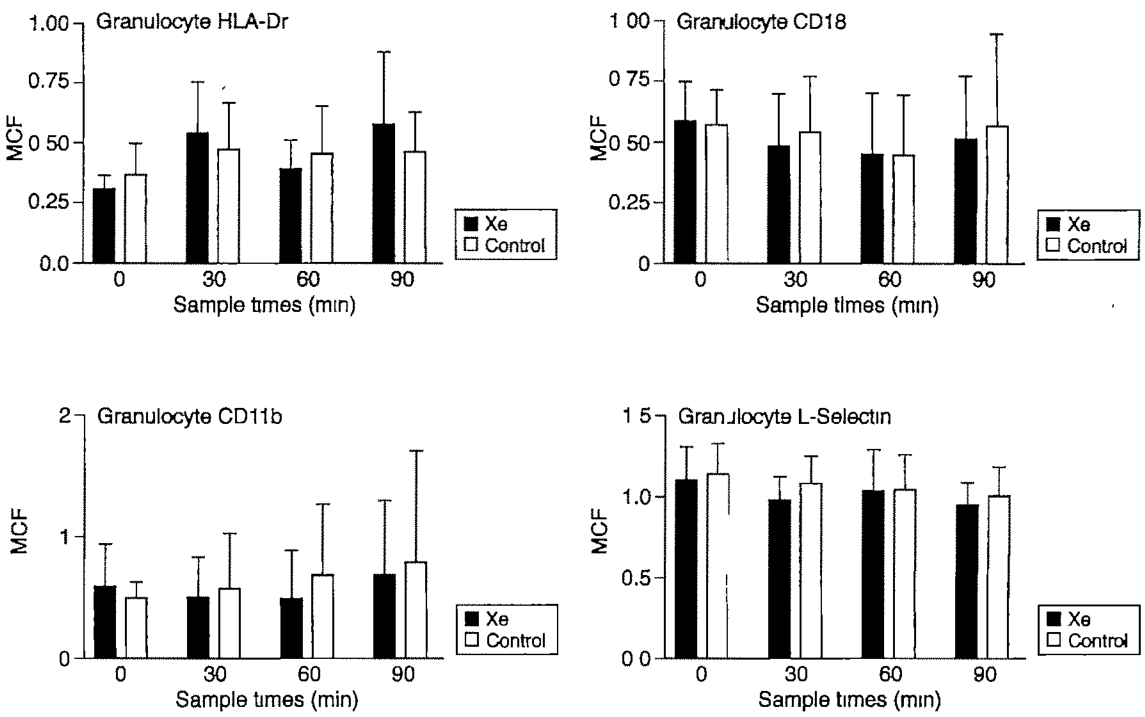


Fig 2 The mean channel fluorescence (MCF), expressed as linear units, of granulocyte HLA-Dr, CD18, CD11b and L-selectin in donor blood at baseline (time 0) and after 30, 60 and 90 min of isolated CPB with xenon in oxygen, and with oxygen-enriched air (control) The error bars represent 1 SD.

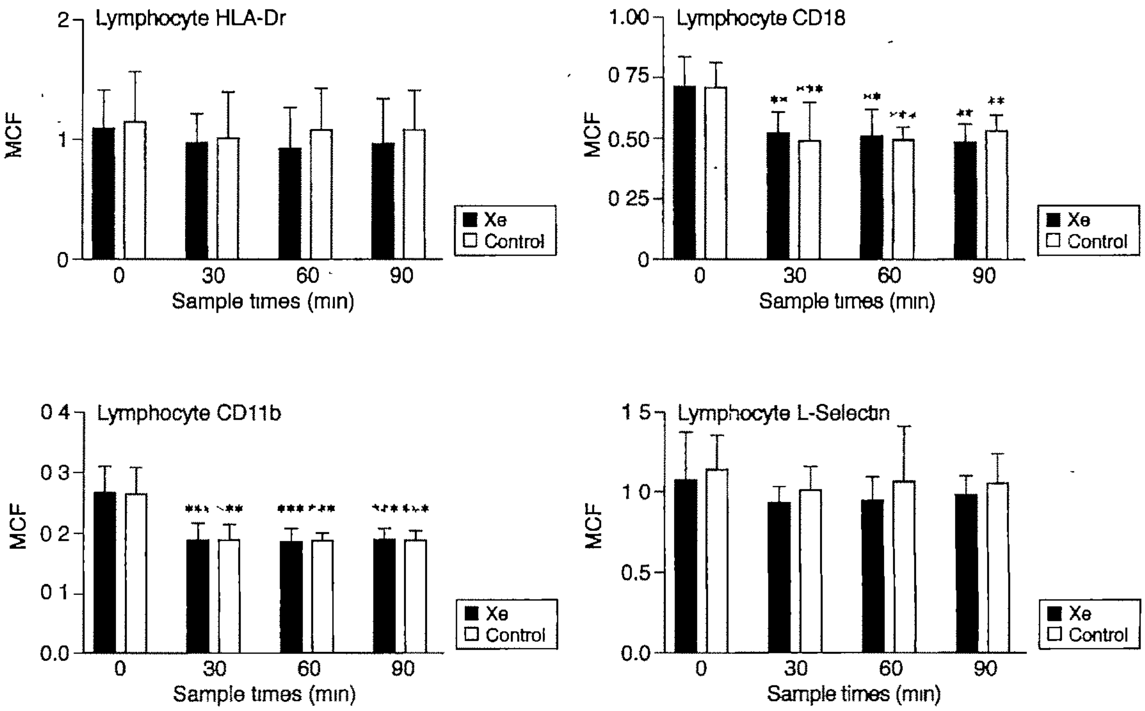


Fig 3 The mean channel fluorescence (MCF), expressed as linear units, of lymphocyte HLA-Dr, CD18, CD11b and L-selectin in donor blood at baseline (time 0) and after 30, 60 and 90 min of isolated CPBwith xenon in oxygen, and with oxygen-enriched air (control) The error bars represent 1 SD. Significant differences from time 0: ***P*<0.01; ****P*<0.001

version 3.0. Adhesion molecule expression and cytokine data were normally distributed and were analysed using repeated measures ANOVA and Bonferroni's post-test correction. The number of bypass experiments done was based on a previous similar study[5] in which 10 bypass experiments were needed to show a difference in IL-8 levels

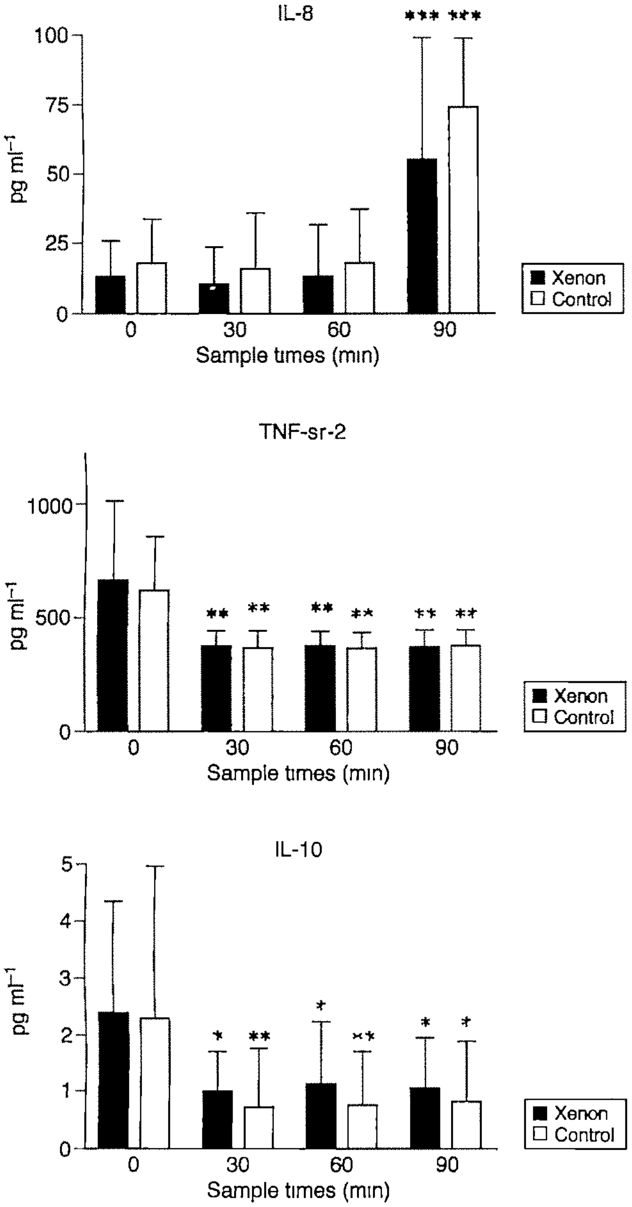
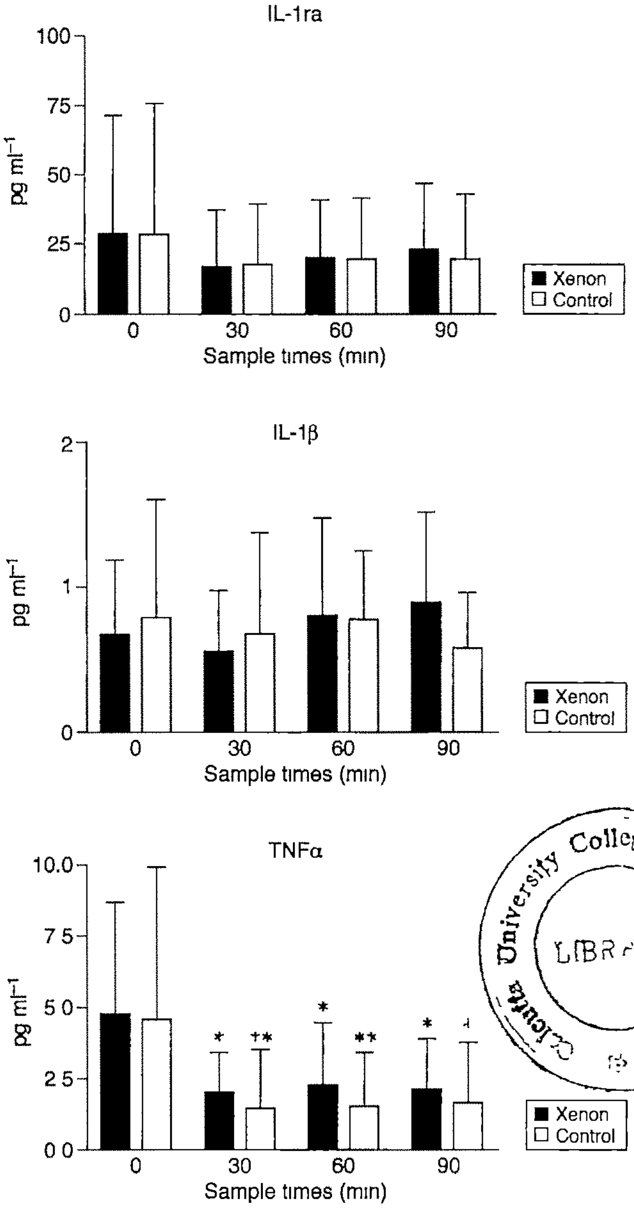


Fig 4 Plasma IL-8, TNF-sr-2, and IL-10 levels (pg ml^{-1}) at baseline (time 0) and after 30, 60 and 90 min of isolated CPB with xenon in oxygen, and with oxygen-enriched air (control). The error bars represent 1 SD Significant differences from time 0 *$P<0.05$; **$P<0.01$, ***$P<0.001$



University College LIBR

Fig 5 Plasma IL-1ra, Il-1β, and TNFα levels (pg ml^{-1}) at baseline (time 0) and after 30, 60 and 90 min of isolated CPB with xenon in oxygen and with oxygen-enriched air (control) The error bars represent 1 SD

of 16 pg ml^{-1} after 90 min (power of 90%, $\alpha=0.05$). $P<0.05$ was considered statistically significant.

Results

Leucocyte adhesion molecule expression (HLA-DR, L-selectin, CD18 and CD11b), expressed as the MCF intensity in linear units, before and during simulated CPB is shown for monocytes, granulocytes and lymphocytes in Figures 1–3, respectively There were significant reductions in lymphocyte CD18 and CD11b in both groups during simulated bypass. The expression of HLA-DR in granulocytes increased from baseline in both groups by 90 min of bypass, significantly so ($P<0.05$) in the xenon group, but there were no between-group differences at any time point.

The effect of xenon on the pro-inflammatory cytokines IL-1β, TNFα, IL-8 and the anti-inflammatory cytokines IL-10, IL-1ra and TNF-sr-2 is shown in Figures 4 and 5, respectively. Compared with baseline, in both groups, at 90 min, IL-8 concentrations were significantly elevated (two samples were excluded from statistical analysis because of a technical error), TNF-sr-2 concentrations were significantly reduced after the start of simulated bypass and IL-10 levels decreased in both groups during bypass IL-1ra was unchanged in both groups during bypass compared with baseline. IL-1β concentrations also showed no within- or between-group differences. TNFα levels decreased after the start of bypass to below the limit of the assay. There were no significant differences between the groups for any variable. Qualitative observation during flow cytometry showed a transient reduction in monocytes only, which recovered by 90 min. This was observed in four of the 10 xenon regimens and in five of the 10 control regimens. In all others the cell numbers did not change.

Discussion

During CPB, rapid changes in plasma cytokine concentrations and circulating lymphocyte populations occur. These changes may be affected by pharmacological interventions and anaesthesia.[4–6] The exact mechanisms and clinical significance of the immunomodulatory changes during CPB are not fully understood. During *in vivo* cardiac surgery, blood sampling alone may not be a satisfactory way to evaluate the immunomodulatory effect of any drug. It is known that bone marrow changes during CPB are reciprocal to the blood changes, suggesting that the T cells have gone out of the blood system to the marrow and possibly the lymphatic system.[7] Thus, blood changes may not indicate immunosuppression but rather an appropriate immunological response. For example, many cytokines that increase with CPB can up-regulate expression of high endothelial venule adhesion molecule, a mechanism of translocation of leucocytes from the vascular to the lymphatic compartments.[8 9] Leucocytes affected by the drug under investigation could migrate out of the circulation and escape detection by blood sampling.

One method of overcoming this difficulty is with the isolated CPB model, which has several advantages over *in vivo* blood sampling. Firstly, using the CPB model, changes to leucocyte sub-populations or surface markers reflect changes within the total leucocyte population in the donor blood sample, except for leucocytes which have been lysed during the CPB process or have adhered to the plastic surface. In other words, in the isolated CPB model, functional leucocytes have no hiding place from the investigator.

Secondly, this system simulates several elements of an evolving inflammatory response (complement fixation and IL-8 production as well as up-regulation of leucocyte adhesion molecule). Some extrapolation between these *in vitro* results and clinical effect may be made. In the isolated bypass system, methylprednisolone, a known immunosuppressant, causes an approximately fourfold decrease in plasma IL-8 levels.[5] *In vivo*, a sixfold reduction in IL-8 was found at a similar time point.[10] This difference in magnitude of response between the *in vitro* and *in vivo* situations may be partly explained by the lack of anti-inflammatory response generated by this isolated bypass system.

We did not find significant immunomodulatory effects of xenon in the isolated CPB system. There were no significant between-group differences in HLA-DR or the adhesion molecules, and there were no between-group differences for any cytokine values. The fact that IL-8 concentrations increased significantly from baseline in both groups by 90 min of isolated CPB, and IL-10 and TNF-sr-2 levels decreased in both groups after 15 min of simulated bypass supports our previous descriptions of the inflammatory response in this model and shows an inflammatory challenge. The adhesion molecule L-selectin is decreased in all cell lines in the xenon regimen compared with the control regimen. This did not achieve statistical significance at any point but is a trend that merits further investigation.

Our results suggest that, as far as immunomodulation is concerned, xenon appears as safe as oxygen-enriched air.

References

1 Franks NP, Dickinson R, de Sousa SL, Hall AC, Lieb WR. How does xenon produce anaesthesia? *Nature* 1998; **396**: 324

2 Petzelt C, Taschenberger G, Schmehl W, Kox WJ. Xenon-induced inhibition of Ca^{2+}-regulated transitions in the cell cycle of human endothelial cells. *Eur J Physiol* 1999; **437**: 737–44

3 Petzelt C, Taschenberger G, Schmehl W, Hafner M, Kox WJ. Xenon induces metaphase arrest in rat astrocytes. *Life Sci* 1999; **65**: 901–13

4 McBride WT, Armstrong MA, Crockard AD, McMurray TJ, Rea JM. Cytokine balance and immunosuppressive changes at cardiac surgery: contrasting responses between patients and isolated CPB circuits. *Br J Anaesth* 1995; **75**: 724–33

5 Gormley SMC, Armstrong MA, McMurray TJ, McBride WT. The effect of methylprednisolone on the immune response using an isolated cardiopulmonary bypass circuit. *Anesth Analg* 1999; **88**(4S): SCA 17

6 Gilliland HE, Armstrong MA, Uprichard S, Clarke G, McMurray TJ. The effect of aprotinin on interleukin-8 concentration and leukocyte adhesion molecule expression in an isolated cardiopulmonary bypass system. *Anaesthesia* 1999; **54**: 427–33

7 Ide H, Kakiuchi T, Furuta N, *et al.* The effect of cardiopulmonary bypass on T-cells and their subpopulations – changes in their proportion in peripheral blood. *Nippon Kyobu Geka Gakkai Zasshi* 1987; **35**· 1089–95

8 Gallatin WM, Weissman IL, Butcher EC. A cell-surface molecule involved in organ-specific homing of lymphocytes. *Nature* 1983; **304**: 30–4

9 Ise Y, Yamaguchi K, Sato K, *et al.* Molecular mechanisms underlying lymphocyte recirculation. I. Functional, phenotypical and morphological characterization of high endothelial cells cultured in vitro. *Eur J Immunol* 1988; **18**: 1235–44

10 Gormley SMC, Armstrong MA, McMurray TJ, MacGowan SW, McBride WT. Methylprednisolone reduces plasma IL8 and urinary anti-inflammatory cytokines at cardiac surgery. *Br J Anaesth* 1999; **82**. A53

British Journal of Anaesthesia **89** (4) 551–5 (2002)

Comparison of ocular microtremor and bispectral index during sevoflurane anaesthesia[†]

L. G. Kevin[1]*, A. J. Cunningham[1] and C. Bolger[2]

[1]Department of Anaesthesia, Beaumont Hospital, Dublin 9, Ireland. [2]Department of Neurosurgery, Beaumont Hospital, Dublin 9, Ireland

**Corresponding author: Leo G. Kevin, Department of Anesthesiology, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226, USA*

Background. A practical and reliable monitor of depth of anaesthesia would be a major advance on current clinical practice. None of the present monitors is both simple to use and accurate. Ocular microtremor (OMT) is a physiological tremor that is suppressed by propofol in a dose-dependent manner. We studied OMT during propofol induction and nitrous oxide–oxygen–sevoflurane maintenance of anaesthesia in 30 patients, and compared OMT with the bispectral index (BIS) as a predictor of response to verbal command.

Methods. OMT was measured using the closed-eye piezoelectric strain-gauge technique. OMT and BIS were measured at specific times during the anaesthetic, including at loss of consciousness, at end-tidal sevoflurane 1 and 2%, and at emergence.

Results. OMT decreased significantly after induction, did not decrease as end-tidal sevoflurane was increased from 1 to 2%, and increased at emergence in all patients. By logistic regression, OMT was more sensitive and specific than BIS in distinguishing the awake from the anaesthetized state (OMT, 84.9 and 93.1% respectively; BIS, 75.7 and 69.0%).

Conclusions. OMT is suppressed by sevoflurane and accurately predicts response to verbal command. OMT may be a useful monitor of depth of hypnosis.

Br J Anaesth 2002; **89**; 551–5

Keywords: anaesthesia, depth; anaesthetics volatile, sevoflurane; eye, ocular microtremor; monitoring, bispectral index

Accepted for publication: May 22, 2002

Current estimation of intraoperative depth of anaesthesia is an inexact science. Autonomic activity (heart rate, sweating, lacrimation) and movement to incision are commonly used as indicators of inadequate anaesthesia. However these clinical signs do not predict depth of sedation.[1] Whilst the electroencephalogram (EEG) may be the most accurate monitor of deep sedation, subtle changes may be difficult to detect and may be non-specific, affected by factors such as temperature, arterial carbon dioxide (Pa_{CO_2}) and electrolyte fluctuations. Additional EEG-based technologies, including spectral edge frequency and the bispectral index (BIS), have been developed but have not demonstrated the accuracy and ease of use required to gain widespread acceptance. At least part of the difficulty likely is that monitors may measure only one of several components of anaesthesia, such as level of sedation or responsiveness to noxious stimuli. The BIS has been consistently reported to be a good general measure of sedation,[2] [3] and whilst the manufacturer of the BIS monitor makes no claim about BIS as an overall measure of anaesthetic depth, it is used for this purpose by many practitioners. However, there are concerns that BIS recordings may be affected by specific drugs in contradictory and unpredictable ways,[4] [5] so that individual patients may risk awareness at BIS levels lower than any defined threshold of unconsciousness.[6] These and other concerns have stimulated the continued search for alternative monitors.

High-frequency eye tremor, or ocular microtremor (OMT), is a physiological tremor of the eye present in all subjects and is related to tonic activity in brainstem oculomotor neurones.[7] First described by Alder and Fliegelman in 1934,[8] this phenomenon attracted scant attention for several decades. More recently it has been shown that the frequency of OMT in patients with head injury correlates with the level of consciousness.[9] Coakley

---

[†] No financial support was received for this work

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

and colleagues studied the effects of anaesthesia on OMT, which was suppressed by thiopentone.[10] In a recent study[11] propofol caused dose-dependent suppression of OMT, suggesting that OMT may indicate the cerebral effect of propofol.

We set out to study the effect of sevoflurane anaesthesia on OMT and to compare OMT with BIS as a predictor of response to verbal command.

Methods

After institutional ethics committee approval and with informed, written consent, we studied 30 patients (mean age 38.0 yr, range 17–59 yr) of ASA status I and II undergoing extracranial surgery under general anaesthesia. Exclusion criteria were age <18 and >60 yr, intracranial or ocular disease and previous ocular surgery.

Baseline BIS and OMT measurements were made before induction of anaesthesia. The A-2000® BIS monitoring system (software 4.0) (Aspect Medical Systems, Natick, MA, USA) was used, and Zipprep® electrodes (Aspect Medical Systems) were applied to the skin in the frontotemporal montage as recommended by the manufacturer.[12] OMT was measured using the piezoelectric strain gauge technique (EyeTect, Belleville, IL, USA), described previously.[13] Briefly, the sensor consists of a probe composed of a surface-mounted amplifier and a piezoelectric transducer which is coated in silicone rubber, and can detect eye movements corresponding to displacement of the sclera ranging from 12 to more than 3000 nm. The probe is applied gently to the closed eyelid for approximately 1 min. The signal from the sensor was amplified, low-pass filtered at 150 Hz and displayed on an oscilloscope (Fluke 123 Industrial Scopemeter; Fluke Industrial, Almelo, The Netherlands). Measurements were made in real time at specific times, using an averaged 3 s segment of OMT waves. We kept a hard copy of each measurement for later examination to ensure readings were free from possible interference from signals such as facial muscle activity and electrocautery.

Patients received a standardized anaesthetic that included premedication with temazepam 20 mg 1 h before surgery. Anaesthesia was induced with i.v. fentanyl 1 $\mu g\ kg^{-1}$ and propofol 2–2.5 $mg\ kg^{-1}$. End-tidal anaesthetic agent concentration was measured routinely by anaesthetic machine monitors (Dräger Cato, Lübeck, Germany). Muscle relaxation was assessed visually by train-of-four ratio (TOFR) using a peripheral nerve stimulator (Ministim IIIA; Life-Tech, Stafford, TX, USA). OMT and BIS readings were recorded manually at the following times, taking a single figure read off each monitor: (1) before induction; (2) at loss of consciousness (first failure to respond to verbal command); (3) immediately before incision; (4) at end-tidal sevoflurane 1% after 10 min of equilibration; (5) at end-tidal sevoflurane 2% after 10 min of equilibration; and (6) at emergence (first response to verbal command). Values at time-points 1, 2, 3 and 6 were made without reference to end-tidal sevoflurane. Every 20 s patients were asked to squeeze an independent observer's hand until failure to respond (at induction) or first unequivocal response to command (at emergence). The study plan did not specify the choice of analgesic agent but most patients received supplementary fentanyl in response to changes in heart rate and arterial pressure. OMT and BIS data were not used to guide patient management. Patients were interviewed 1 day after surgery to identify cases of explicit recall.

Data analysis

Data are expressed as medians and interquartile values. Comparison of the variables at each time was with the Wilcoxon matched-pairs signed-ranks test. The abilities of OMT and BIS to distinguish the awake state (defined by response to verbal command) from the asleep state (loss of response after induction) and the steady-state asleep state (end-tidal 2% sevoflurane) from the awake state (first response at emergence) were compared using logistic regression models; sensitivity, specificity, positive predictive values and negative predictive values of the indices for the data set were determined, and receiver operating characteristic curves were derived. Analyses were performed using Stata 3.1 (College Station, TX, USA). After Bonferroni correction, $P<0.05$ was considered statistically significant.

Results

We studied 30 patients (18 males, mean age 38 yr, range 17–59 yr). OMT frequency decreased significantly at loss of consciousness (first failure to respond to verbal command): [85 (82–88) (awake) *vs* 48 (39–52) Hz, $P<0.001$], as did BIS [92 (90–96) *vs* 74 (65–80), $P<0.001$]. There were no significant differences for OMT between the time-points of loss of consciousness, pre-incision and end-tidal sevoflurane 1 and 2% (Fig. 1). BIS decreased significantly between loss of consciousness and pre-incision but did not differ significantly between end-tidal sevoflurane 1 and 2% (Fig. 2). OMT gave better logistic regression models than BIS to discriminate between the awake state and loss of consciousness at the beginning of anaesthesia, and to discriminate between the anaesthetized patient (end-tidal sevoflurane 2%) and the patient after recovery. Performance values for OMT and BIS models at return of consciousness are shown in Table 1 and the receiver operating characteristic curves are shown in Figures 3 and 4.

Neuromuscular block was used in 10 patients included in the study. OMT signals were not obliterated by these agents (even at TOFR=0), and although OMT amplitude decreased significantly (by 40–60%), amplitude remained sufficient for accurate measurement of OMT frequency, which was unaffected by neuromuscular block. Four patients among 20

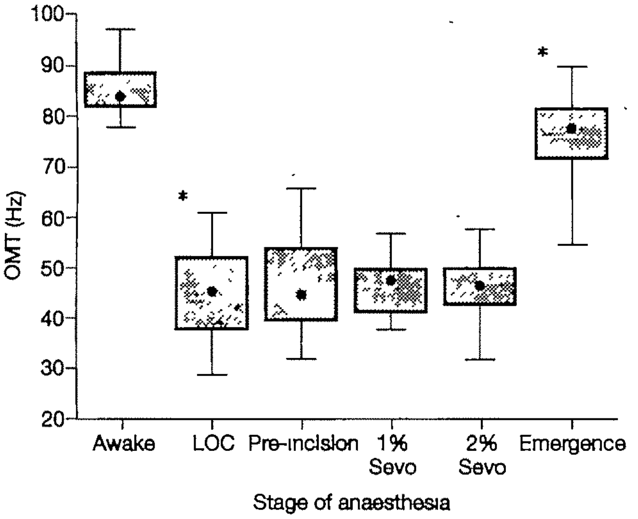


Fig 1 Ocular microtremor (OMT) at each time-point in temporal sequence (n=30). The boxes represent the median (point) and interquartile (25, 75) values The extended bars represent the entire range. A=awake; L=first loss of response to verbal command; I=before surgical incision; 1%=end-tidal sevoflurane 1%; 2%=end-tidal sevoflurane 2%; E=first response to verbal command. *P<0.001.

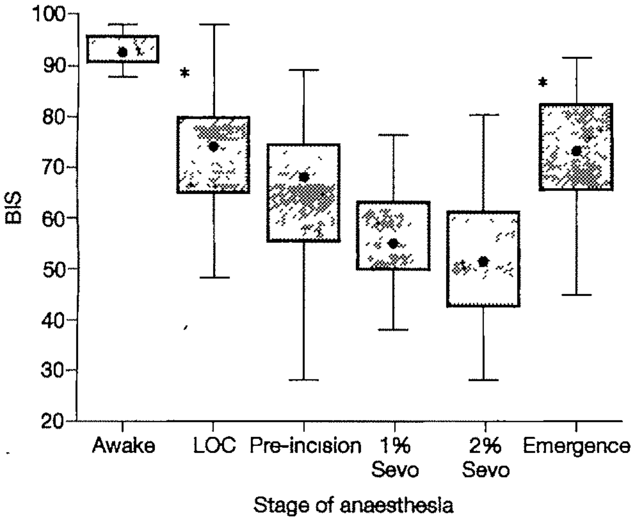


Fig 2 Bispectral index (BIS) at each time-point in temporal sequence (n=30). The boxes represent the median (point) and interquartile (25, 75) values. The extended bars represent the entire range. A=awake, L=first loss of response to verbal command, I=before surgical incision; 1%=end-tidal sevoflurane 1%; 2%=end-tidal sevoflurane 2%; E=first response to verbal command *P<0.001.

who did not receive neuromuscular blocking agents moved at the time of skin incision. OMT frequency was significantly higher before incision in patients who moved compared with those who did not move (P<0.05), whereas BIS did not differ significantly between these patients. No patient reported recall of intra-operative events despite specific questioning on the day after surgery.

Table 1 Performance values (%) for logistic regression models of ocular microtremor (OMT) and bispectral index (BIS) to distinguish the asleep (end-tidal sevoflurane 2%) from the awake state at emergence (first response to verbal command)

	OMT	BIS
Sensitivity	85	76
Specificity	94	69
Positive predictive value	93	74
Negative predictive value	84	71

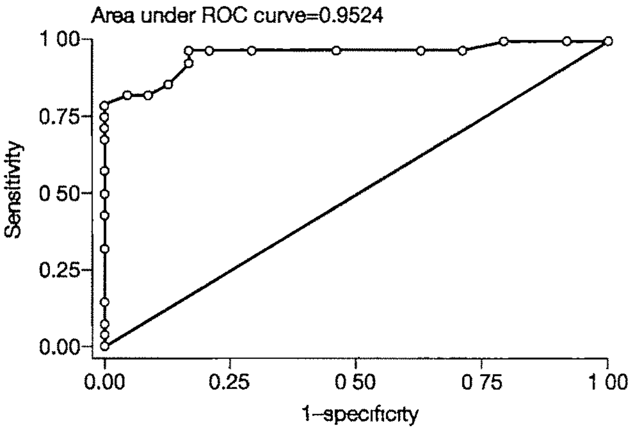


Fig 3 Receiver operating characteristic (ROC) curve for OMT to discriminate the steady-state asleep state (at end-tidal 2% sevoflurane) from the awake state (first response at emergence) The area under the curve provides a measure of the discriminatory performance of the model. An area of 1 indicates 100% accuracy and an area of 0.5 indicates performance no better than chance; the central diagonal line indicates an area of 0.5.

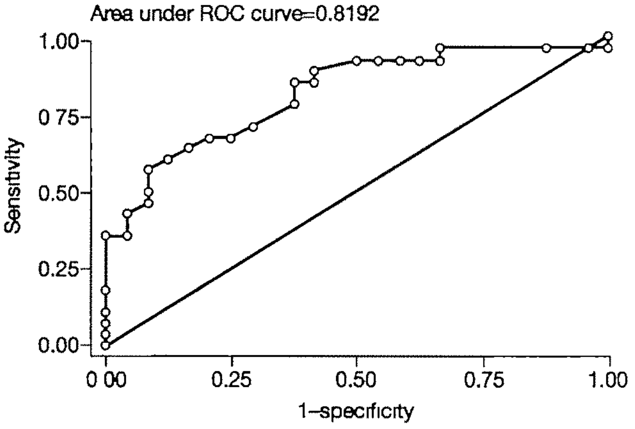


Fig 4 Receiver operating characteristic (ROC) curve for BIS to discriminate steady-state anaesthesia (at end-tidal 2% sevoflurane) from the awake state (first response at emergence).

Discussion

The i.v. anaesthetic agents thiopentone[10] and propofol[11] suppress OMT, suggesting that OMT may be useful as a marker of unconsciousness. The effects of volatile anaesthetic agents on OMT have not been studied previously. The primary objective of this study was to assess the effect of volatile anaesthetic on OMT and the secondary objective was to compare OMT with BIS, a device that is used currently to monitor depth of anaesthesia. We found that OMT is suppressed by sevoflurane. Compared with BIS, there was less overlap between conscious and unconscious values at induction of anaesthesia, and less of a hysteresis effect at emergence, allowing more accurate identification of the patient who has regained consciousness. Importantly, OMT was still measurable even during profound neuromuscular block (TOFR=0). OMT may therefore allow the identification of the conscious but paralysed patient.

The piezoelectric strain-gauge technique to measure OMT was first described in 1968.[14] Measurements are relatively easy to obtain and to date records have been obtained from more than 250 normal subjects and patients. In previous reports, OMT readings were obtained by placing a piezoelectric probe on the anaesthetized sclera.[9–11 14] In our study the probe was placed over the closed eyelid. This is comfortable for the patient and reproducible results can be obtained. No cases of scleral or other eye damage have been noted during use of the open-eye technique and we expect that the closed-eye technique will give even greater safety.

We chose i.v. induction with propofol and the opioid fentanyl to assess the monitoring techniques under conditions reflecting routine clinical practice. It is difficult to quantify the effects of propofol and fentanyl (and other administered opioids) on OMT, although the duration of surgery in most of our patients and the reported effect on OMT of stopping propofol[11] suggest that sevoflurane was predominantly responsible for the continued suppression of OMT during surgery. An increase in end-tidal sevoflurane from 1 to 2% did not further decrease OMT. The lack of effect may reflect the number or variety of patients studied or other confounding factors, such as choice of analgesic agent and intensity of surgical stimulus. It may be a real effect, indicating either that the increase in end-tidal concentration was insufficient to cause a change in OMT or that sevoflurane, when administered in sufficient concentrations to achieve unconsciousness, produces an all-or-none type response in OMT.

We excluded patients less than 18 and greater than 60 yr old. In adults, normal OMT frequency is known to be 84 (SD 6) Hz,[15] and in subjects more than 70 yr of age the mean peak count frequency is approximately 7 Hz lower than in younger subjects.[15] There are no published OMT data in children. Thresholds to define unconsciousness may require adjustment for age which cannot be defined by the present data. Parkinson's disease,[16] multiple sclerosis[17] and head injury[9] alter OMT. As suggested previously,[11] a more useful threshold to define unconsciousness may be a percentage reduction from the patient's baseline OMT.

We chose to compare OMT with the BIS, an EEG-derived measure of the hypnotic component of anaesthesia. In bispectral analysis, EEG waves are initially subjected to a Fourier transform and the phase correlation of the resulting sine waves is then analysed.[18] Other EEG features are then combined using an algorithm that gives a single measurement, the BIS. The BIS is on a scale of dimensionless units in which 100 represents the awake state, 70 deep sedation and 60 general anaesthesia, continuing to 0, which indicates isoelectric EEG. In several studies (as in our study), BIS predicted the ability of patients undergoing anaesthesia to respond to command.[19 20] Furthermore, BIS correlates with end-tidal sevoflurane concentration[20] and measured blood propofol concentration.[21] However, the BIS value required to ensure unresponsiveness and suppression of memory formation varies greatly between studies,[22] and a recent report highlights the possibility of explicit awareness at BIS values generally taken to indicate unconsciousness reliably.[6] A further difficulty in the determination of specific BIS thresholds is the marked hysteresis effect.[2 23] In other words, BIS values associated with unconsciousness at induction of anaesthesia commonly occur with consciousness during emergence. This effect leads to risk of awareness if anaesthetic drug doses are titrated using a specific value. We noted this effect, which also occurred to some extent with OMT, as demonstrated by logistic regression analysis. As reported elsewhere,[2] BIS tended to rise gradually as anaesthesia was lightened at the end of surgery. In contrast, OMT tended to remain depressed until just before the first response to verbal command. These results suggest that BIS can provide a graded measure of impending emergence. However, OMT may exclude the aware patient more accurately. In the only other controlled study of anaesthetic effects on OMT,[11] OMT readings at emergence are not reported.

We did not observe a statistically significant effect on BIS of increasing end-tidal sevoflurane from 1 to 2%, although there was a trend towards decreased BIS. We may not have studied a sufficient number of patients to find this effect as it is likely to be small. Katoh and co-workers report that BIS does not show further decreases when end-tidal sevoflurane concentration exceeds 1.4%.[20]

In summary, both OMT and BIS decreased at induction and remained depressed during sevoflurane anaesthesia. When using response to verbal command to indicate consciousness, OMT showed less overlap between the conscious and unconscious states and more accurately identified patients regaining consciousness after anaesthesia. OMT is depressed by i.v. and inhalational anaesthetic agents and recordings can be obtained from a probe placed over the closed eyelid. Further studies are needed of this technique at extremes of age, in patients with pre-existing central nervous system pathology and during different surgical procedures.

Acknowledgement

Eye probes were provided free of charge by EyeTect, LLC (Belleville, IL, USA).

References

1 Domino KB, Posner KL, Caplan RA, Cheney FW. Awareness during anesthesia: a closed claims analysis. *Anesthesiology* 1999; **90**: 1053–61

2 Gajraj RJ, Doi M, Mantzaridis H, Kenny GN. Comparison of bispectral EEG analysis and auditory evoked potentials for monitoring depth of anaesthesia during propofol anaesthesia. *Br J Anaesth* 1999; **82**: 672–8

3 Iselin-Chaves IA, Flaishon R, Sebel PS, *et al.* The effect of the interaction of propofol and alfentanyl on recall, loss of consciousness, and the bispectral index. *Anesth Analg* 1998; **87**: 949–55

4 Vernon JM, Lang E, Sebel PS, Manberg P. Prediction of movement using bispectral electroencephalographic analysis during propofol/alfentanyl or isoflurane/alfentanyl anesthesia. *Anesth Analg* 1995; **80**: 780–5

5 Detsch O, Schneider G, Kochs E, Hapfelmeier G, Werner C. Increasing isoflurane concentration may cause paradoxical increases in the EEG bispectral index in surgical patients. *Br J Anaesth* 2000; **84**: 33–7

6 Mychaskiw G, Horowitz M, Sachdev V, Heath BJ. Explicit intraoperative recall at a bispectral index of 47. *Anesth Analg* 2001; **92**: 808–9

7 Coakley, D. *Minute Eye Movement and Brain Stem Function.* Florida: CRC Press, 1983; 49–56.

8 Alder FH, Fliegelman F. The influence of fixation on the visual acuity. *Arch Ophthalmol* 1934; **12**: 475–83

9 Coakley D, Thomas JG. The ocular microtremor record and the prognosis of the unconscious patient. *Lancet* 1977; **1**: 512–5

10 Coakley D, Thomas JG, Lunn JN. The effect of anaesthesia on ocular microtremor. *Br J Anaesth* 1976; **48**: 1121–2

11 Bojanic S, Simpson T, Bolger C. Ocular microtremor: a tool for measuring depth of anaesthesia? *Br J Anaesth* 2001; **86**: 519–22

12 Aspect Medical Systems. *BIS Clinical Reference Manual.* Natick, USA: Aspect Medical Systems, 1997

13 Sheahan NF, Coakley D, Hegarty F, Bolger C, Malone J. Ocular microtremor measurement system: design and performance. *Med Biol Eng Comput* 1993; **31**: 205–12

14 Benji H, Thomas JG. Three electronic methods for recording ocular tremor. *Med Biol Eng* 1968; **6**: 171–8

15 Bolger C, Bojanic S, Sheahan NF, Coakley D, Malone JF. Dominant frequency content of ocular microtremor from normal subjects. *Vision Res* 1999; **39**: 1911–5

16 Bolger C, Bojanic S, Sheahan NF, Coakley D, Malone JF. Ocular microtremor in patients with idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1999; **66**: 528–31

17 Bolger C, Bojanic S, Sheahan NF, Malone J, Hutchinson M, Coakley D. Ocular microtremor (OMT): a new neurophysiological approach to multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2000, **68**: 639–42

18 Sigl J, Camoun NG. An introduction to bispectral analysis for the electroencephalogram. *J Clin Monit* 1994; **10**: 392–404

19 Liu J, Singh H, White PF. Electroencephalographic bispectral index correlates with intraoperative recall and depth of propofol-induced sedation. *Anesth Analg* 1997, **84**: 185–9

20 Katoh T, Suzuki A, Ikeda K. Electroencephalographic derivatives as a tool for predicting the depth of sedation and anesthesia induced by sevoflurane. *Anesthesiology* 1998; **88**: 642–50

21 Glass PS, Bloom M, Kearse L, Rosow C, Sebel P, Manberg P. Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanyl in healthy volunteers. *Anesthesiology* 1997; **86**: 836–47

22 Drummond JC. Monitoring depth of anaesthesia *Anesthesiology* 2000; **93**: 876–82

23 Sleigh JW, Donovan J. Comparison of bispectral index, 95% spectral edge frequency and approximate entropy of the EEG, with changes in heart rate variability during induction of general anaesthesia. *Br J Anaesth* 1999; **82**: 666–71

British Journal of Anaesthesia **89** (4): 556–61 (2002)

Randomized, double-blind comparison of different inspired oxygen fractions during general anaesthesia for Caesarean section[†]

W. D. Ngan Kee[1*], K. S. Khaw[1], K. C. Ma[2], A. S. Y. Wong[1] and B. B. Lee[1]

[1]Department of Anaesthesia and Intensive Care, [2]Department of Paediatrics, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong, China

**Corresponding author*

Background. The optimal inspired oxygen fraction $F\text{I}_{O_2}$ for fetal oxygenation during general anaesthesia for Caesarean section is not known.

Methods. We randomized patients having elective Caesarean section to receive one of the following: $F\text{I}_{O_2}$ 0.3, $F\text{I}_{N_2O}$ 0.7 and end-tidal sevoflurane 0.6% (Group 30, *n*=20); $F\text{I}_{O_2}$ 0.5, $F\text{I}_{N_2O}$ 0.5 and end-tidal sevoflurane 1.0% (Group 50, *n*=20), or $F\text{I}_{O_2}$ 1.0 and end-tidal sevoflurane 2.0% (Group 100, *n*=20) until delivery. Neonatal outcome was compared biochemically and clinically.

Results. At delivery, for umbilical venous blood, mean $P\text{O}_2$ was greater in Group 100 (7.6 (SD 3.7) kPa) compared with both Group 30 (4.0 (1.1) kPa, $P<0.0001$) and Group 50 (4.7 (0.9) kPa, $P=0.002$) and oxygen content was greater in Group 100 (17.2 (1.6) ml dl^{-1}) compared with both Group 30 (12.8 (3.6) ml dl^{-1}, $P=0.0001$) and Group 50 (13.8 (2.6) ml dl^{-1}, $P=0.0001$). For umbilical arterial blood, $P\text{O}_2$ was greater in Group 100 (3.2 (0.4) kPa) compared with Group 30 (2.4 (0.7) kPa, $P=0.003$), and in Group 50 (2.9 (0.8) kPa) compared with Group 30 (2.4 (0.7) kPa, $P=0.04$); oxygen content was greater in Group 100 (10.8 (3.5) ml dl^{-1}) than in Group 30 (7.0 (3.0) ml dl^{-1}, $P<0.01$). Apgar scores, neonatal neurologic and adaptive capacity scores, and maternal arterial plasma concentrations of epinephrine and norepinephrine before induction and at delivery were similar among groups. No patient reported intraoperative awareness.

Conclusions. Use of $F\text{I}_{O_2}$ 1.0 during general anaesthesia for elective Caesarean section increased fetal oxygenation.

Br J Anaesth 2002; **89**: 556–61

Keywords: anaesthesia, depth; anaesthesia, obstetric; anaesthetics volatile, sevoflurane; oxygen, inspired concentration; partial pressure, oxygen

Accepted for publication: April 2, 2002

The optimum inspired oxygen fraction $F\text{I}_{O_2}$for general anaesthesia for Caesarean section is unclear. Early papers suggested that an $F\text{I}_{O_2}$ of 0.5, combined with 50% nitrous oxide and a low concentration of a volatile agent was optimum,[1] and this continues to be the most commonly used technique in the United Kingdom.[2] However, subsequent reports have advocated both smaller[3] and greater[4 5] values of $F\text{I}_{O_2}$.

The different findings may result from differences in study design. Confounding factors that make interpretation of earlier studies difficult include lack of lateral uterine displacement,[6 7] inclusion of both labouring and non-labouring patients,[3–5] incomplete or undescribed methods of randomization[3 5–8] and inadequate compensation for changes in anaesthetic depth when varying $F\text{I}_{O_2}$.[3 6–8] Furthermore, previous studies used umbilical arterial and venous $P\text{O}_2$ to calculate fetal haemoglobin oxygen saturation, taking into account the characteristics of the fetal oxyhaemoglobin concentration curve.[5] No previous study has directly measured the effect of maternal $F\text{I}_{O_2}$ on umbilical cord blood oxygen content.

[†]Presented in part as a free paper at the 10th European Society of Anaesthesiologists and 24th European Academy of Anaesthesiology meeting, Nice, France, April 2002.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

We set out to compare the effect of FI_{O_2} of 0.3, 0.5 and 1.0 on umbilical cord blood oxygen content in patients having elective Caesarean section under general anaesthesia. To achieve equivalent depth of anaesthesia among groups, we calculated equipotent doses of inhaled anaesthetics and measured and closely regulated circuit anaesthetic concentrations. Because light anaesthesia can increase maternal circulating catecholamines and cause uteroplacental vasoconstriction,[4 5] we measured maternal arterial plasma concentrations of epinephrine and norepinephrine before induction and at delivery. Neonatal outcome was compared biochemically by measurement of umbilical venous and arterial blood gases and oxygen content using co-oximetry, and clinically by assessment of neonatal Apgar scores and neurologic and adaptive capacity scores (NACS).

Methods

After obtaining approval from the Clinical Research Ethics Committee of the Chinese University of Hong Kong, we consecutively recruited 60 ASA I and II women with term singleton pregnancies having elective Caesarean section under general anaesthesia. All patients gave written informed consent. Patients with pre-existing or pregnancy-induced hypertension, cardiovascular or cerebrovascular disease or known fetal abnormalities were excluded.

Patients were given oral ranitidine 150 mg the night before and on the morning of surgery and 30 ml 0.3 M sodium citrate on arrival in the operating theatre. Standard monitoring included non-invasive arterial pressure measurement, electrocardiography and pulse oximetry. A wide-bore i.v. catheter was inserted under local anaesthesia and a slow infusion of lactated Ringer's solution was started. Patients were then randomly allocated to one of three groups by drawing of sequentially numbered sealed envelopes that each contained a computer-generated randomization code. Each group received a different inspired oxygen fraction during the period from immediately after induction to delivery.

The circuit oxygen analyser was calibrated immediately before each case and lateral uterine displacement was achieved by tilting the operating table to the left. After pre-oxygenation, rapid sequence induction with cricoid pressure was achieved using thiopental 4 mg kg^{-1} and succinylcholine 1.5 mg kg^{-1}. Atracurium was given as required for further muscle relaxation as indicated by a peripheral nerve stimulator. The lungs were ventilated to maintain end-tidal carbon dioxide concentration of 4.3 kPa. For maintenance of anaesthesia, we used sevoflurane[9] as the volatile agent because of its low blood–gas partition coefficient. Concentrations of oxygen, nitrous oxide and sevoflurane were adjusted according to group allocation: Group 30 received FI_{O_2} 0.3, FI_{N_2O} 0.7 and sevoflurane adjusted to maintain end-tidal concentration of 0.6%; Group 50 received FI_{O_2} 0.5, FI_{N_2O} 0.5 and end-tidal sevoflurane 1.0%; and Group 100 received FI_{O_2} 1.0 and end-tidal sevoflurane 2.0%. These inspired fractions were chosen to provide approximately equivalent MAC values. A circle circuit with a fresh gas flow of 6 litre min^{-1} was used and for all patients the sevoflurane vaporizer was initially set at 6% for the first 60 s in order to prime the circuit and was then adjusted as required to maintain the allocated end-tidal concentration. Oxygen and anaesthetic concentrations were measured using the modules integrated into the anaesthesia machine (Narkomed 4, North American Dräger, Telford, PA, USA). All monitoring data were downloaded to a Macintosh computer using software developed within our department.

Patients were not informed of the group allocation. One anaesthetist was responsible for controlling the delivery of the anaesthetic. Separate investigators were responsible for the blood sampling and analysis. To mask these investigators and the surgeon to the treatment, the anaesthesia machine was turned away so the monitors were not visible to them. Maternal arterial haemoglobin oxygen saturation was measured continuously using pulse oximetry. The contingency plan for any patient who developed an Sp_{O_2} 95% was to increase the FI_{O_2} to the next highest group, and for any patient who developed hypotension was to increase the rate of i.v. fluid administration. Times of skin incision, uterine incision and delivery were recorded by stopwatch.

Approximately 10 ml maternal arterial blood was taken by radial artery puncture before pre-oxygenation and at the time of delivery. Each sample was divided into aliquots for measurement of blood gases, oxygen content and plasma concentrations of epinephrine and norepinephrine. Samples of arterial and venous blood were taken from a double-clamped segment of umbilical cord for measurement of blood gases and oxygen content. After delivery, morphine 0.15 mg kg^{-1} and oxytocin 10 IU were given i.v. Anaesthesia was then maintained using FI_{O_2} 0.3, FI_{N_2O} 0.7 and end-tidal sevoflurane 0.6% in all patients.

After delivery, the neonate was assessed by a paediatrician (KCM) who was not aware of the treatment, who recorded Apgar scores 1 min and 5 min after birth and NACS 15 min and 2 h after birth.

At the end of surgery, residual neuromuscular block was antagonized using neostigmine and atropine. Blood loss was assessed by measuring blood in the suction bottle minus liquor, weighing wet swabs and estimating blood on drapes and on the floor.

Each patient was visited on the first day after operation by a research nurse, who asked the patient if she was able to recall any intraoperative events or remembered any dreams during the operation.

Laboratory analyses

All blood samples were drawn into heparinized syringes. Samples for blood-gas and oxygen-content analysis were immediately placed in ice. Blood gases were measured using a Ciba-Corning 278 Blood Gas System blood gas analyser (Ciba-Corning, Medfield, MA, USA). Oxygen content and total haemoglobin concentration were measured using an IL 482 Co-oximeter (Instrumentation Laboratory, Lexington, MA, USA) with correction for 70% fetal haemoglobin. Blood samples for catecholamine analysis were immediately put into lithium-heparin tubes containing metabisulphite as an antioxidant and the tubes were immediately placed in ice. These were centrifuged at 4°C and the plasma was separated and stored at –70°C pending batch analysis. Norepinephrine and epinephrine were measured by high performance liquid chromatography. Catecholamines were extracted with alumina, analysed on a reverse-phase Ultrasphere IP C18 column (Beckman Instruments Inc., Altex Division, San Ramon, CA, USA) and detected by an electrochemical method on an ESA 5100A coulometric detector (Environmental Science Associates, Bedford, MA, USA). The within-day coefficients of variation for norepinephrine and epinephrine were 7.06% and 8.48%, respectively, and the between-day coefficients of variation were 10.69% and 12.69%, respectively. The assay was linear to the lower limit of detection, which was 25 pg ml^{-1} for both norepinephrine and epinephrine.

Statistics

Prospective power analysis was based on data from our previously published work.[10] The primary outcome was defined as the umbilical venous oxygen content. We calculated that a sample size of 17 patients per group would have 90% power to detect a 20% difference in oxygen content among groups with an alpha value of 0.05. To allow for possible difficulties with sample collection, we increased the sample size to 20 per group. Intergroup comparisons were made using analysis of variance with post-hoc pairwise comparisons using Scheffe's procedure. Single-variable intragroup comparisons were made using the paired *t*-test. Nominal data were analysed using the chi square test and Fisher's exact test. Analyses were performed using Statview for Windows 4.53 (Abacus Concepts Inc., Berkeley, CA, USA). $P<0.05$ was considered significant.

Results

Patient recruitment took 2 yr and 7 months, from October 1998 to April 2001. The relatively long time required to complete data collection reflects the low usage of general anaesthesia for Caesarean section in our unit (approximately 12% for elective cases during the study period). The indications for general anaesthesia were similar among groups and included placenta praevia (36), patient refusal of regional anaesthesia (20), and contraindication for regional anaesthesia because of low platelet count, antiplatelet medication or spinal deformity (4). Patient characteristics and surgical details were similar among groups (Table 1).

Table 1 Patient characteristics and surgical times. Values are mean (SD or range)

	Group 30 (*n*=20)	Group 50 (*n*=20)	Group 100 (*n*=20)	*P*
Age (yr)	34 (27–41)	34 (26–41)	35 (27–43)	0.8
Weight (kg)	65 (9)	64 (10)	66 (5)	0.8
Height (cm)	157 (5)	156 (4)	157 (5)	0.9
Induction to delivery time (min)	12.2 (5.5)	11.4 (2.3)	13.3 (4.7)	0.4
Uterine incision to delivery time (s)	97 (39)	85 (35)	103 (48)	0.4
Estimated blood loss (ml)	795 (413)	626 (310)	821 (564)	0.4

In general, F_{IO_2} and anaesthetic concentration could be well maintained in the target ranges, although it was noted that for patients in Group 100, F_{IO_2} of exactly 1.0 was difficult to achieve because of the diluting presence of other gases and vapours. No patient required an increase of the allocated F_{IO_2} because of a low S_{PO_2}.

There was insufficient sample volume for analysis from one patient in Group 30 for umbilical venous blood, from one patient in Group 50 for maternal arterial blood and from two patients in Group 50 and three patients in Group 100 for umbilical arterial blood. The paediatrician investigator (KCM) was not available for three cases in Group 30, three in Group 50 and one in Group 100; in these cases the neonate was assessed by the duty paediatrician, who assessed Apgar scores but not NACS.

No patient reported recall of intraoperative events. One patient in Group 50 reported experiencing intraoperative dreams but was not distressed by this.

Maternal arterial blood gases, haemoglobin concentration and oxygen content are shown in Table 2. Values for P_{aO_2} at delivery increased with increasing F_{IO_2}, but there was no difference in maternal arterial oxygen content among groups or between baseline and delivery values within groups.

Umbilical cord gases and haemoglobin concentration are shown in Table 3 and oxygen content is shown in Figure 1. P_{O_2} was significantly different among groups for both umbilical venous ($P<0.0001$) and arterial ($P=0.002$) blood. Post-hoc analysis showed that for umbilical venous blood, P_{O_2} was greater in Group 100 than in Group 30 ($P<0.0001$) and in Group 100 compared with Group 50 ($P=0.002$). For umbilical arterial blood, P_{O_2} was greater in Group 100 than in Group 30 ($P=0.003$) and in Group 50 compared with Group 30 ($P<0.05$). There were no differences between groups in pH or P_{CO_2}. Oxygen content of umbilical blood was significantly different between groups for both venous ($P<0.0001$) and arterial blood ($P<0.01$). Post-hoc analysis showed that for umbilical venous blood, mean oxygen content was greater in Group 100 than in Group 30 (17.2 (SD 1.6) *vs* 12.8 (3.6) ml dl^{-1}, $P=0.0001$) and in Group 100 compared with Group 50 (17.2 (1.6) *vs* 13.8 (2.6) ml dl^{-1}, $P=0.0001$). For umbilical arterial blood, oxygen content was

Table 2 Maternal arterial blood gases, haemoglobin concentration and oxygen content. *P* values shown are from analysis of variance. Significant results from post-hoc analysis are indicated as different compared with Group 100 (***$P<0.001$) and different compared with Group 50 (‡$P<0.001$). Values are mean (SD)

	Group 30 (*n*=20)	Group 50 (*n*=20)	Group 100 (*n*=20)	*P*
Baseline				
pH	7.45 (0.02)	7.44 (0.02)	7.45 (0.02)	0.4
Pa_{CO_2} (kPa)	4.0 (0.3)	4.2 (0.3)	4.0 (0.4)	0.2
Pa_{O_2} (kPa)	14.7 (3.5)	14.1 (1.2)	14.4 (2.3)	0.7
Haemoglobin concentration (g dl^{-1})	10.9 (1.0)	11.3 (1.3)	11.3 (1.1)	0.4
Oxygen content (ml dl^{-1})	14.8 (1.4)	15.3 (1.8)	15.3 (1.6)	0.6
Delivery				
pH	7.41 (0.03)	7.43 (0.04)	7.41 (0.03)	0.4
Pa_{CO_2} (kPa)	4.3 (0.4)	4.4 (0.4)	4.4 (0.4)	0.4
Pa_{O_2} (kPa)	19.8 (3.1)***‡	31.5 (8.0)***	60.9 (10.1)	<0.0001
Haemoglobin concentration (g dl^{-1})	10.5 (0.9)	10.8 (1.1)	11.0 (2.3)	0.6
Oxygen content (ml dl^{-1})	14.5 (1.5)	14.2 (2.0)	14.4 (1.9)	0.9

Table 3 Umbilical cord blood gases and haemoglobin concentration. *P* values shown are from analysis of variance. Significant results from post-hoc analysis are indicated as different compared with Group 100 (**$P<0.01$, ***$P<0.001$) and compared with Group 50 (†$P<0.05$). Values are mean (SD)

	Group 30 (*n*=20)	Group 50 (*n*=20)	Group 100 (*n*=20)	*P*
Umbilical venous				
pH	7.34 (0.03)	7.36 (0.03)	7.35 (0.04)	0.3
$P\text{CO}_2$ (kPa)	5.8 (0.6)	5.8 (0.4)	5.5 (0.6)	0.3
$P\text{O}_2$ (kPa)	4.0 (1.1)***	4.7 (0.9)**	7.6 (3.7)	<0.0001
Haemoglobin concentration (g dl^{-1})	14.4 (1.3)	13.7 (1.4)	14.0 (1.2)	0.3
Umbilical arterial				
pH	7.31 (0.03)	7.32 (0.04)	7.30 (0.03)	0.2
$P\text{CO}_2$ (kPa)	6.8 (0.7)	6.5 (0.7)	6.8 (0.6)	0.4
$P\text{O}_2$ (kPa)	2.4 (0.7)**†	2.9 (0.8)	3.2 (0.4)	0.002
Haemoglobin concentration (g dl^{-1})	14.2 (1.5)	13.6 (1.5)	14.2 (2.4)	0.5

greater in Group 100 than in Group 30 (10.8 (3.5) *vs* 7.0 (3.0) ml dl^{-1}, $P<0.01$).

The results of clinical assessment of the neonates are shown in Table 4. There was no difference among groups in the proportion of Apgar scores <7 at 1 min. All neonates had Apgar scores ≥7 at 5 min. NACS were similar among groups at 15 min and at 2 h. Eight neonates in Group 30, three in Group 50 and five in Group 100 required a brief period of assisted mask ventilation immediately after birth ($P=0.2$); of these, one neonate in Group 30 and one neonate in Group 100 required tracheal intubation for suction. Three neonates were admitted to the neonatal intensive care unit: two in Group 100 because of tachypnoea and one in Group 30 because of cyanosis on feeding. In none of these cases was the admission considered to be related to the anaesthetic technique.

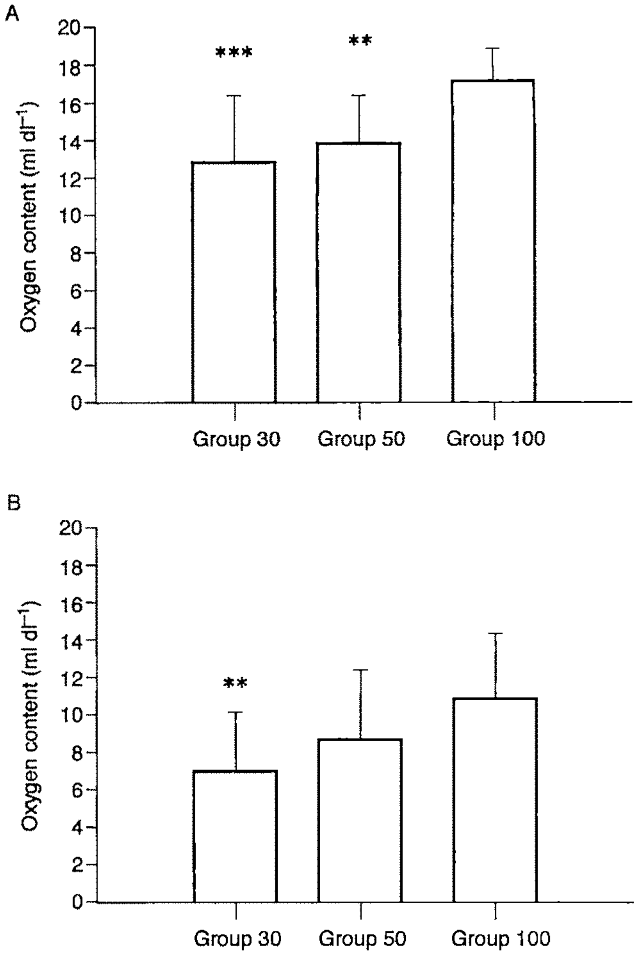


Fig 1 Umbilical venous (A) and arterial (B) cord blood oxygen content. **$P<0.01$, significantly different from Group 100. ***$P<0.001$, significantly different from Group 100

Maternal arterial catecholamine concentrations are shown in Table 5. In each group, maternal arterial plasma concentrations of epinephrine were higher at delivery than at baseline (all $P<0.05$). Similarly, in each group, plasma concentrations of norepinephrine were higher at delivery than at baseline (all $P<0.01$). However, there were no differences in plasma concentrations of either epinephrine or norepinephrine between groups at either baseline or at delivery.

Discussion

Our study showed that in patients having general anaesthesia using nitrous oxide and sevoflurane, oxygen transfer to the fetus was greatest with the use of an $F\text{I}_{\text{O}_2}$ near 1.0 compared with $F\text{I}_{\text{O}_2}$ of 0.5 and 0.3. This was reflected by a greater umbilical venous oxygen content in Group 100 compared with Group 30 and Group 50 and greater umbilical arterial oxygen content in Group 100 compared with Group 30.

Table 4 Clinical neonatal outcome. Values for neurologic and adaptive capacity score (NACS) are mean (SD)

	Group 30 (*n*=20)	Group 50 (*n*=20)	Group 100 (*n*=20)	*P*
Apgar score at 1 min				
4–6 (*n*)	7	3	5	0.3
≥7 (*n*)	13	17	15	0.3
Apgar score at 5 min				
4–6 (*n*)	0	0	0	
≥7 (*n*)	20	20	20	
Assisted ventilation required at birth (*n*)	8	3	5	0.2
Admitted to neonatal intensive care (*n*)	1	0	2	0.3
NACS at 15 min	31.5 (4.7)	32.8 (3.6)	31.7 (4.8)	0.7
NACS at 2 h	35.8 (3.3)	36.9 (1.9)	36.0 (3.3)	0.5

Table 5 Maternal arterial plasma catecholamine concentrations. Values are mean (SD)

	Group 30 (*n*=20)	Group 50 (*n*=20)	Group 100 (*n*=20)	*P*
Baseline				
Epinephrine (pg ml^{-1})	142 (63)	154 (85)	122 (76)	0.4
Norepinephrine (pg ml^{-1})	275 (103)	362 (223)	307 (131)	0.2
Delivery				
Epinephrine (pg ml^{-1})	203 (92)	292 (279)	223 (143)	0.3
Norepinephrine (pg ml^{-1})	451 (150)	501 (281)	483 (277)	0.8

These findings support the earlier work by Bogod, Piggott and colleagues,[4 5] who also reported that the use of 100% oxygen improved fetal oxygenation compared with 50% oxygen. As 100% oxygen increased umbilical venous oxygen tension, they postulated that because of the high oxygen affinity of fetal haemoglobin, this should correspond to a significant increase in oxygen content. We have confirmed this by measuring oxygen content using co-oximetry. Bogod, Piggott and colleagues also emphasized the importance of adjusting the concentration of volatile anaesthetic to compensate for loss of the anaesthetic contribution from nitrous oxide. This was not done in previous studies[6 7] and it was suggested that light anaesthesia could have increased plasma catecholamines and caused placental vasoconstriction.[4 5] In our study we found no difference between groups in maternal arterial plasma concentrations of epinephrine and norepinephrine, making it unlikely that differences in depth of anaesthesia contributed to any differences in cord blood results. However, the small sample size should be noted in the interpretation of these data. Retrospective power analysis showed that our study had 80% power to detect a 44% difference in maternal arterial plasma norepinephrine concentration and a 65% difference in maternal arterial plasma epinephrine concentration in Group 100 compared with the other groups.

In our study, similar to those of Bogod, Piggott and colleagues, we calculated and administered equivalent MAC values of inhalational anaesthetics to each group. We also initially administered a high concentration of volatile agent to rapidly increase alveolar anaesthetic concentration. However, we limited this initial period of overpressure to only 1 min, compared with 5 min in the previous studies. Thereafter we titrated anaesthetic delivery according to end-tidal concentration, which was not done in the previous studies. This was facilitated by our choice of sevoflurane, because its low blood–gas partition coefficient results in rapid changes of alveolar concentration. In retrospect, we might have been further able to confirm equivalent depth of anaesthesia among groups by use of bispectral index (BIS) monitoring, although few data are available on BIS monitoring in pregnant patients.

Previously, Lawes and colleagues[3] investigated different values of $F_{I_{O_2}}$ during general anaesthesia for Caesarean section. In contrast to our findings, they found no difference in umbilical venous P_{O_2} in patients who received an $F_{I_{O_2}}$ of 0.33 compared with patients who received an $F_{I_{O_2}}$ of 0.5. However, that study was not fully randomized and was only partially blinded, there was no compensatory adjustment of isoflurane concentration, and both labouring and non-labouring patients were included. Although the authors concluded that use of 33% oxygen appeared to be safe, they did not include a group that received an $F_{I_{O_2}}$ of 1.0 for comparison.

Perreault and colleagues[11] investigated administration of 100% oxygen during the period between hysterotomy and birth during general anaesthesia for Caesarean section. Compared with a group that received 50% oxygen, they found no difference in umbilical venous or arterial P_{O_2}. Notably, however, no adjustment of volatile anaesthetic was made after discontinuing nitrous oxide in the 100% group and four out of 10 patients reported intraoperative awareness. This serves to emphasize the importance of increasing the concentration of volatile agent and monitoring circuit concentration when using 100% oxygen. In that study, two infants in the 100% group had low early Apgar scores, which was not explained.

We found no difference in the clinical condition of the neonates, assessed using Apgar scores and NACS. However, significant differences would be difficult to detect in healthy uncomplicated elective cases in whom outcome was already expected to be favourable. Further research is required to determine whether the increase in oxygen delivery we found in elective cases could lead to differences in clinical outcome in emergency cases when there is fetal distress. Such an advantage was suggested by Piggott and colleagues[5] who found that neonates born to mothers who received 100% oxygen during emergency Caesarean section had a smaller requirement for oxygen and positive-pressure ventilation compared with those delivered to mothers who received 50% oxygen. We chose to use NACS as a method of evaluating potential differences among groups exposed to different anaesthetic combinations, including relatively high concentrations of sevoflurane and found no difference between groups. Retrospective power analysis showed that our study had 80% power to detect a mean difference in NACS score of 4 points at 15 min and 3 points at 2 h in Group 100 compared with the other groups. However, since this study was planned, the validity of NACS has been questioned.[12 13]

Finally, although we have found that a high $F_{I_{O_2}}$ improved fetal oxygenation, the potential harmful effects of oxygen should be considered. Maternal hyperoxia could provoke vasoconstriction in the fetoplacental unit.[14] However, our finding that fetal oxygenation improved in the group that received the highest $F_{I_{O_2}}$ suggests that this is not a significant concern in elective cases. Hyperoxia also increases the rate of formation of toxic reactive species by superoxide generation.[15] In a previous study[16] we found that a high $F_{I_{O_2}}$ during regional anaesthesia for Caesarean section resulted in increased maternal and umbilical plasma concentrations of lipid peroxide markers of oxygen free-radical activity. The clinical importance of this is as yet undetermined. We are now investigating the effect of $F_{I_{O_2}}$ on markers of free-radical generation during general anaesthesia for Caesarean section.

Acknowledgements

The authors thank the midwives of the Labour Ward, Prince of Wales Hospital, Shatin, Hong Kong, China and research nurses Justina Liu, Floria Ng and Mabel Wong for their assistance with this study. This work was supported by a Direct Grant for Research from the Chinese University of Hong Kong

References

1 Moir DD. Anaesthesia for Caesarean section. An evaluation of a method using low concentrations of halothane and 50 per cent oxygen *Br J Anaesth* 1970; **42**: 136–42

2 Thurlow JA, Kinsella SM. Maternal inspired oxygen fraction for Caesarean section under general anaesthesia. *Int J Obstet Anesth* 2001; **10**: 229

3 Lawes EG, Newman B, Campbell MJ, Irwin M, Dolenska S, Thomas TA. Maternal inspired oxygen concentration and neonatal status for Caesarean section under general anaesthesia. Comparison of effects of 33% or 50% oxygen in nitrous oxide. *Br J Anaesth* 1988; **61**: 250–4

4 Bogod DG, Rosen M, Rees GAD. Maximum $F_{I_{O_2}}$ during Caesarean section. *Br J Anaesth* 1988; **61**. 255–62

5 Piggott SE, Bogod DG, Rosen M, Rees GAD, Harmer M. Isoflurane with either 100% oxygen or 50% nitrous oxide in oxygen for Caesarean section. *Br J Anaesth* 1990; **65**: 325–9

6 Baraka A. Correlation between maternal and foetal P_{O_2} and P_{CO_2} during Caesarean section. *Br J Anaesth* 1970; **42**: 434–8

7 Rorke MJ, Davey DA, Du Toit HJ. Foetal oxygenation during Caesarean section. *Anaesthesia* 1968; **23**: 585–96

8 Marx GF, Mateo CV. Effects of different oxygen concentrations during general anaesthesia for elective Caesarean section. *Can Anaesth Soc J* 1971; **18**: 587–93

9 Gambling DR, Sharma SK, White PF, Van Beveren T, Bala AS, Gouldson R. Use of sevoflurane during elective Cesarean birth: a comparison with isoflurane and spinal anesthesia. *Anesth Analg* 1995; **81**: 90–5

10 Gin T, Ngan Kee WD, Siu YK, Stuart JC, Tan PE, Lam KK. Alfentanil given immediately before the induction of anesthesia for elective Cesarean delivery. *Anesth Analg* 2000; **90**. 1167–72

11 Perreault C, Blaise GA, Meloche R. Maternal inspired oxygen concentration and fetal oxygenation during Caesarean section. *Can J Anaesth* 1992; **39**: 155–7

12 Brockhurst NJ, Littleford JA, Halpern SH. The Neurologic and Adaptive Capacity Score: a systematic review of its use in obstetric anesthesia research. *Anesthesiology* 2000; **92**: 237–46

13 Camann W, Brazelton TB Use and abuse of neonatal neurobehavioral testing. *Anesthesiology* 2000; **92**: 3–5

14 Crawford JS. Fetal well-being and maternal awareness. *Br J Anaesth* 1988; **61**: 247–9

15 Knight PR, Holm BA. The three components of hyperoxia. *Anesthesiology* 2000; **93**: 3–5

16 Khaw KS, Wang CC, Ngan Kee WD, Pang CP, Roger MS. High-inspired oxygen fraction during elective Caesarean section under spinal anaesthesia induces lipid-peroxidation in the mother and fetus. *Br J Anaesth* 2002; **88**: 18–23

British Journal of Anaesthesia **89** (4): 562–5 (2002)

Epinephrine and clonidine do not improve intrathecal sufentanil analgesia after total hip replacement[†]

R. Fournier*, E. Van Gessel, A. Weber and Z. Gamulin

Department of Anaesthesiology, University Hospital of Geneva, CH-1211 Geneva 14, Switzerland
**Corresponding author: Département d'Anesthésiologie, Hôpital Cantonal Universitaire, CH-11 Genève 14, Switzerland*

Background. We compared analgesia after intrathecal sufentanil alone, sufentanil with epinephrine 200 µg and sufentanil with clonidine 30 µg in patients after total hip replacement, the endpoints being onset and duration of action.

Methods. We performed a randomized double-blind study of 45 patients for elective total hip arthroplasty using continuous spinal anaesthesia. As soon as a pain score higher than 3 on a 10 cm visual analogue scale was reported, sufentanil 7.5 µg alone, sufentanil 7.5 µg + epinephrine 200 µg or sufentanil 7.5 µg + clonidine 30 µg in 2 ml normal saline was given intrathecally. Pain scores, rescue analgesia (diclofenac and morphine) and adverse effects (respiratory depression, postoperative nausea and vomiting, itching) were observed for 24 h after surgery.

Results. Time to a pain score of <3 [6 (SD 1) *vs* 6 (1) *vs* 5 (1) min], time to the lowest pain score [7 (2) *vs* 8 (2) *vs* 8 (2) min] and time to the first dose of systemic analgesic for a pain score >3 [281 (36) *vs* 288 (23) *vs* 305 (30) min] were similar in all three groups. Adverse effects and analgesic requirements during the first 24 h were also similar.

Conclusion. After total hip replacement, all three analgesic regimens gave good analgesia with comparable onset and duration of action, and minor adverse effects.

Br J Anaesth 2002; **89**: 562–6

Keywords: analgesics opioid, sufentanil; sympathetic nervous system, clonidine; sympathetic nervous system, epinephrine

Accepted for publication: September 19, 2001

Intrathecal (i.t.) opioid analgesia is widely used in labour[1 2] and is also used after general surgery.[3 4] Spinal lipophilic opioids, such as fentanyl, sufentanil and nalbuphine,[4 5] give prompt and profound analgesia compared with the slow onset of action of i.t. morphine.[5] I.T. sufentanil provides nearly instantaneous pain relief, but its duration of action is relatively short in labour (60–90 min),[6 7] whereas the analgesic effect is longer when this opioid is administered for postoperative pain relief after total hip replacement (240 min).[4]

A longer duration of analgesia after i.t. sufentanil would be useful for patients undergoing orthopaedic surgery. A longer action might be obtained by adding either epinephrine or clonidine, as found in obstetrics, in which epinephrine (200 µg)[2] and clonidine (30 µg)[10] mixed with sufentanil significantly prolong analgesia.

In this double-blind, randomized study we compared the speed of onset and duration of action after i.t. administration of sufentanil 7.5 µg alone and mixed with either epinephrine 200 µg or clonidine 30 µg for postoperative pain relief in elderly patients undergoing total hip arthroplasty.

Methods

After obtaining institutional ethics committee approval and informed consent, we studied 45 patients aged more than 70 yr, ASA physical status II–IV, scheduled for elective total hip replacement. We excluded patients with psychiatric illness, allergy to opiates, the study drugs or local anaesthetics, severe chronic obstructive respiratory disease (forced expiratory volume in 1 s <600 ml) or coagulation disorders. On the basis of previous studies,[1 4 8] we expected analgesia to be prolonged for 60 min, giving a standardized difference of 1.3. To detect a prolongation in duration of

---

[†] Presented in part at the Annual Meeting of the American Society of Anesthesiology, San Francisco, October 2000

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Table 1 Patient characteristics [mean (SD or range), n=15 for each group]. ASA, American Society of Anesthesiologists, SUF, sufentanil; SUF+EPI, sufentanil plus epinephrine; SUF+CLO, sufentanil plus clonidine

	SUF	SUF + EPI	SUF+CLO
Age (yr)	76 (70–82)	79 (73–85)	78 (71–85)
Height (cm)	167 (8)	163 (10)	166 (8)
Weight (kg)	75 (11)	71 (15)	78 (15)
Females, males	5, 10	10, 5	6, 9
ASA class 2, 3, 4	3, 12, 0	5, 10, 0	4, 11, 0

60 min, 15 patients per group would be needed for β=0.2 and α=0.05.

All patients were given morphine 0.1 mg kg^{-1} s.c. 60 min before the operation, to obviate opioid supplements. These can be needed during surgery because of the prolonged lateral decubitus position, which sometimes causes shoulder pain. In the operating room, an i.v. infusion of lactated Ringer solution was started through a 17 gauge peripheral venous catheter. Electrocardiogram, non-invasive arterial blood pressure and peripheral oxygen saturation were measured and a urinary catheter was inserted. Continuous spinal anaesthesia was administered with the patient in the lateral position, operation side up, at the L2–3 or L3–4 intervertebral space using an 18 gauge Tuohy needle (epidural miniset), and a 20 gauge catheter was inserted 3–4 cm into the subarachnoid space. Injections of 0.5% isobaric bupivacaine 2.5 or 5 mg (Carbostesine®, Astra, Dietikon, Switzerland) were given as required. Surgery was performed to a standard plan.

After surgery, the i.t. catheter was flushed with normal saline 2 ml and left in place. Patients received oxygen by face mask. In the recovery room, when the pain score on the operated side was greater than 3/10 on a visual analogue scale (VAS; 0=no pain at all, 10=unbearable pain), the patients were randomly allocated (by the closed envelope technique) to one of the three study groups: group SUF received sufentanil 7.5 µg (Sufenta®, Janssen-Cilaf, Baar, Switzerland) alone, group SUF+EPI received sufentanil 7.5 µg with epinephrine 200 µg, and group SUF+CLO received sufentanil 7.5 µg with clonidine 30 µg, all in normal saline 2 ml through the i.t. catheter over 30 s. Study drugs were prepared by an anaesthetist who was the only person with access to the randomization list and was not otherwise involved in the study. The first author (RF) injected drugs blindly and tested the patients during the first hour. Afterwards, the patients were tested by the nurse in charge and, after leaving the recovery room, by ward nurses, who collected the data and gave the analgesics according to the study plan. Twenty-four hours after the i.t. opioid injection, one of the authors (RF or ZG) collated the data.

Pain score, sedation score (1=awake and alert; 2=awake but drowsy, responding to a verbal stimulus; 3=drowsy but rousable, responding to a physical stimulus; 4=unrousable, not responding to a physical stimulus), respiratory rate, oxygen saturation and haemodynamic changes were measured at i.t. injection and then every 2.5 min for the first 15 min, every 5 min for the next 45 min and every hour for the next 5 h. We noted times to VAS <3 (onset of action), to the lowest VAS and to the first systemic analgesic intervention (reappearance of hip pain, VAS >3) and recorded ketorolac (Toradol®, Roche, Reinach, Switzerland) and morphine requirements (rescue analgesia given by the systemic route) during the first 24 h after i.t. injection. We recorded side-effects of nausea and/or vomiting, pruritus (grade 1=mild, not disturbing; grade 2=moderate, disturbing but not requiring treatment; grade 3=severe, requiring treatment) and respiratory depression (respiratory rate < 8/min).

Patients could request systemic rescue analgesia if their pain score was still greater than 3/10 30 min after i.t. injection or after the i.t. analgesia regressed. Ketorolac 30 mg i.v. was available first, followed by morphine 0.1 mg kg^{-1} s.c. if the VAS was still greater than 3/10 after 30 min. Afterwards, these analgesics were given on demand (pain score >3) with a maximum of three doses per 24 h for ketorolac and eight doses per 24 h for morphine.

Nausea and/or vomiting were treated with metoclopramide (Primperan®, Synthélabo, Lausanne, Switzerland) 10 mg i.v. and a reduction in mean arterial blood pressure (MAP) by more than 20% of resting value with ephedrine 5 mg i.v. and a rapid infusion of normal saline 250 ml. Clemastine (Tavegil®, Novartis, Bern, Switzerland) 2 mg i.v. was administered for severe pruritus and naloxone (Narcan®, Dupont Pharma, Bad Homburg, Germany) 40 µg i.v. was injected for respiratory depression (respiratory rate <8 b.p.m.). The patients only left the recovery room for the ward after receiving the first rescue analgesia.

Statistical analysis

Data are presented as mean (SD) or median (range) and groups were compared by analysis of variance or the Kruskal–Wallis test as required; a P value of less than 0 05 was considered statistically significant.

Results

Patient characteristics, presented in Table 1, were comparable between groups. No supplementary i.v. opiates or sedatives were administered during surgery.

Pain scores, onset and duration of action of i.t. sufentanil alone and with epinephrine or clonidine are presented in Table 2 and Figures 1 and 2. Results were comparable in the three groups. After i.t. injection, all patients achieved a VAS of 0 (Table 2).

Although a slightly shorter onset and longer duration of action was observed with the sufentanil–clonidine mixture, the differences were not statistically significant (Figs 1 and 2).

Table 2 Pain scores (10-point VAS scale), onset and duration of action in the three groups [mean (SD) or median (range), n=15 for each group] SUF, sufentanil, SUF+EPI, sufentanil plus epinephrine, SUF+CLO, sufentanil plus clonidine

	SUF	SUF+EPI	SUF+CLO
Pain score before injection	5 (4–8)	5 (4–10)	5 (4–9)
Time to pain score <3 (min)	6 (1)	6 (1)	5 (1)
Time to lowest pain score (min)	7 (2)	8 (2)	8 (2)
Time to first systemic analgesic intervention (min)	281 (36)	288 (23)	305 (30)
Lowest pain score	0	0	0
Pain score at 24 h	0 (0–1)	0 (0–2)	0 (0–2)

The analgesic requirements in the first 24 h were similar (Table 3). One patient in the SUF group, two in the SUF+EPI group and two in the SUF+CLO group were not considered for analysis of postoperative analgesic requirements because they received further i.t. analgesia.

The cardiovascular changes in the first hour after i.t. injection were comparable in all groups (Table 4). Ephedrine was given to one patient in the SUF group, two patients in the SUF+EPI group and four patients in the SUF+CLO group.

Respiratory rates less than 8 b.p.m. were not seen. However, one patient in the SUF+EPI group had an oxygen saturation less than 95% for a short time, requiring adjustment of oxygen administration. Four patients in the SUF group, six in the SUF+EPI group and eight in the SUF+CLO group complained of pruritus in the first hour after i.t. injection. Antihistamines were required in two patients in each of the SUF and SUF+EPI groups and in one patient in the SUF+CLO group. Before rescue analgesia, two patients in the SUF group, four in the SUF+EPI group and one in the SUF+CLO group had nausea and/or vomiting requiring antiemetic therapy. Sedation score never exceeded grade 2 in any patients in the first hour after i.t. injection.

Discussion

We believe this is the first study of analgesia from sufentanil–epinephrine and sufentanil–clonidine combinations for postoperative pain relief in patients, apart from obstetrics. All the treatment gave, within 5–6 min, excellent pain relief which lasted for 4.5–5 h. No significant differences between groups were found in the quality of pain relief assessed by VAS pain scores, onset or duration of analgesic action, adverse effects and subsequent analgesic treatment.

We added epinephrine 200 µg to sufentanil, as this dose is commonly used in obstetrics without circulatory effects.[2 6 8] Cardiovascular effects of i.t. clonidine are a serious concern, and in our frail, elderly patients we gave a moderate dose of 30 µg, which seems to prolong the analgesic action of i.t. sufentanil in labour and to have acceptable effects on the circulation.[1]

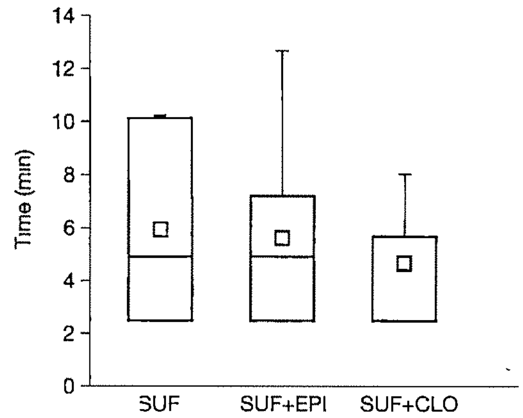


Fig 1 Box plots showing the onset of action (time between initial intrathecal injection and reaching pain score <3) in all groups Open boxes represent the 25th to 75th percentiles and contain the median (horizontal bar) and mean (small square) values, vertical bars represent the 10th to 90th percentiles

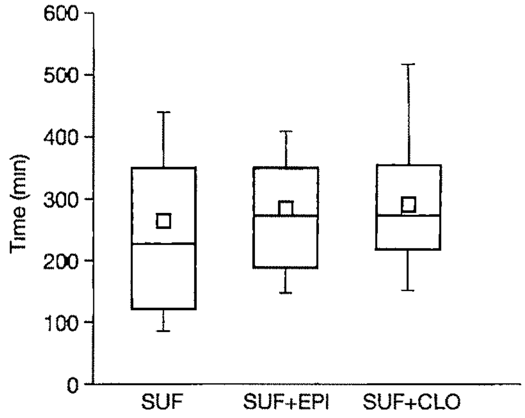


Fig 2 Box plots showing the duration of action [time from initial intrathecal injection to reappearance of a pain score (VAS) of >3, requiring the first systemic analgesic intervention] in all groups Open boxes represent the 25th to 75th percentiles and contain the median (horizontal bar) and mean (small square) values; vertical bars represent the 10th to 90th percentiles.

The prolongation of analgesia by epinephrine has in the past been attributed to vasoconstriction, reducing the clearance of coadministered drugs from the subarachnoid space.[9] However, epinephrine does not reduce the maximal plasma concentration of local anaesthetics.[10 11] An alternative explanation for the prolongation of spinal anaesthesia by vasoconstrictors may be a direct effect on the nociceptive system in the dorsal horn of the spinal cord,[12] where opioids and adrenergic agonists may interact. In cats, the suppression of nociception by fentanyl is increased by epinephrine.[12] In humans, the effects of epinephrine in addition to i.t. sufentanil, which have been only described in labour, are controversial. A study[8] of sufentanil 10 µg i.t. with or without epinephrine 200 µg reported a significant but small prolongation of analgesia from 115 to 132 min, and another

Table 3 Analgesic requirements during the first 24 h after intrathecal injection [mean (SD) or median (range)]. SUF, sufentanil; SUF+EPI, sufentanil plus epinephrine, SUF+CLO, sufentanil plus clonidine

	SUF (n=14)	SUF+EPI (n=13)	SUF+CLO (n=13)
Ketorolac (mg/patient)	30 (23)	37 (29)	33 (20)
Morphine (mg/patient)	11.5 (6)	13(11)	16 (10)
Number of analgesic doses/patient	2.5 (1–5)	3 (1–6)	3 (1–6)

Table 4 Changes in mean arterial pressure (MAP) and heart rate during the first hour after intrathecal injection [mean (SD), n=15 in each group] SUF, sufentanil; SUF+EPI, sufentanil plus epinephrine; SUF+CLO, sufentanil plus clonidine

	SUF	SUF+EPI	SUF+CLO
Baseline MAP (mm Hg)	93 (19)	90 (20)	97 (12)
Maximal decrease in MAP (%)	14 (10)	22 (18)	23 (9)
Time to maximal decrease in MAP (min)	20 (19)	21 (18)	23 (14)
Baseline heart rate (beats min^{-1})	74 (17)	76 (16)	76 (17)
Maximal decrease in heart rate (%)	7 (8)	9 (11)	8 (8)
Time to maximal decrease in heart rate (min)	16 (16)	16 (15)	25 (18)
Ephedrine (number of patients)	1	2	4

showed pain relief for 90 min in both groups.[6] Our data support this finding. Two other studies in labour suggest a more pronounced effect of epinephrine added to a mixture of bupivacaine and sufentanil. Gautier and colleagues[13] found that a small dose of epinephrine (25 µg) added to bupivacaine 1 mg and sufentanil 5 µg i.t. prolonged the analgesia by about 40 min. Campbell and colleagues[2] added a larger dose of epinephrine 200 µg to sufentanil 10 µg and bupivacaine 2.5 mg, and reported a prolongation of 43 min. Adding epinephrine to a mixture of local anaesthetic and opioids seems more efficient in prolonging analgesia than adding it to sufentanil alone, and the reason for this is not clear.

We found only a trend to prolongation of pain relief in the SUF+CLO group compared with the control SUF group (305 *vs* 281 min), whereas the addition of clonidine 30 µg to sufentanil 5 µg prolonged labour analgesia from 99 to 145 min[1] and from 97 to 125 min.[14] These differences may be related to the different type of pain, with an increasing and changing pattern during labour (somatic to visceral) compared with postoperative pain, which tends to decrease with time. Compared with labour analgesia, the pain relief in our elderly patients lasted 281 (36) min and the addition of clonidine 30 µg was probably not enough to improve the analgesia provided by sufentanil 7.5 µg alone. A larger dose of clonidine, e.g. 50 µg, might have provided a longer duration of pain relief, as demonstrated by d'Angelo and colleagues,[15] who found labour analgesia lasting 197 min after adding clonidine 50 µg to sufentanil 7.5 µg and bupivacaine 2.5 mg, and 132 min for sufentanil—bupivacaine.

Clonidine extends labour analgesia when added to i.t. opioids, but causes hypotension.[1 13 14 16 17] The incidence of hypotension was doubled by adding clonidine 30 µg to sufentanil 5 µg (25 *vs* 50%).[1] Mercier and colleagues found that 63% of patients developed hypotension with the same analgesic regimen.[14] Sia reported a decrease in blood pressure in 60% of parturients receiving bupivacaine 1.25 mg, sufentanil 5 µg and clonidine 30 µg compared with only 7% in a control group without clonidine.[16] We found a maximal decrease in MAP, from the baseline value, of 22 and 23% in the SUF+EPI and SUF+CLO groups respectively, compared with 14% in the SUF control group (Table 4). The trend towards greater hypotension in the SUF+CLO group is not surprising,[1 14] but a 22% decrease in blood pressure after adding epinephrine has not been described previously. Apart from profound analgesia reducing sympathetic activity, no other explanation is evident. The number of patients in this study may have been insufficient to detect other cardiovascular effects.

Pruritus was noted in 40% (18 out of 45 patients), with no differences between the groups. Severe itching requiring antihistamines occurred in five patients (11%).

These data are consistent with our previous report[4] and well below the 80–100% observed in obstetric studies.[1 2] Pregnant women may be more susceptible than elderly patients, possibly for hormonal reasons. Epinephrine did not decrease the incidence of pruritus in our patients, contrary to Camman and colleagues' study, in which pruritus was reduced by 50% in the epinephrine group.[6]

Postoperative nausea and/or vomiting was not statistically different between groups. We found no greater incidence in the SUF+EPI group, in contrast to the finding of Camman and colleagues (0% without epinephrine *vs* 35% with epinephrine).[6]

In conclusion, after total hip replacement, i.t. sufentanil alone or mixed with epinephrine or clonidine provides excellent analgesia (a pain score of 0 was achieved in all patients investigated), with comparable onset and duration of action. Clonidine and epinephrine tend to decrease blood pressure, so we do not recommend adding these agents to sufentanil.

References

1 Gautier PE, De Kock M, Fanard L, Van Steenberge A, Hody JL Intrathecal clonidine combined with sufentanil for labor analgesia. *Anesthesiology* 1998; **88**: 651–6

2 Campbell DC, Banner R, Crone LA, Gore-Hickman W, Yip RW. Addition of epinephrine to intrathecal bupivacaine and sufentanil for ambulatory labor analgesia. *Anesthesiology* 1997; **86**: 525–31

3 Gulnard P, Chiolero R, Mavrocordatos P, Carpenter R. Prolonged intrathecal analgesia via a 32 gauge catheter after thoracotomy. *Anesth Analg* 1993; **77**· 936–41

4 Fournier R, Van Gessel E, Weber A, Gamulin Z A comparison of intrathecal analgesia with fentanyl or sufentanil after total hip replacement. *Anesth Analg* 2000; **90**: 918–22

5 Fournier R, Van Gessel E, Macksay M, Gamulin Z. Intrathecal

morphine versus nalbuphine for postoperative pain relief after total hip replacement. *Acta Anaesthesiol Scand* 2000; **44**: 940–5

6 Camman WR, Mintzer BH, Denney RA, Datta S. Intrathecal sufentanil for labor analgesia. Effects of added epinephrine. *Anesthesiology* 1993; **78**: 870–4

7 Herman NL, Calicott R, Van Decar TK, Conlin G, Tilton J. Determination of the dose–response relationship for intrathecal sufentanil in laboring patients. *Anesth Analg* 1997; **84**: 1256–61

8 Grieco WM, Norris MC, Leighton BL *et al.* Intrathecal sufentanil labor analgesia: the effects of adding morphine or epinephrine. *Anesth Analg* 1993; **77**: 1149–54

9 Covino BG, Lambert DH. Epidural and spinal anesthesia. In: Barash PG, Cullen BF, Stoelting RK, eds. *Clinical Anesthesia.* Philadelphia: J. B. Lippincott, 1992, 828–40

10 Abouleish E, Rawal N, Tobon-Randal B, Rivera-Weiss M, Wu A, Rashad MN. A clinical and laboratory study to compare the addition of 0.2 mg of morphine, 0.2 mg of epinephrine, or their combination to hyperbaric bupivacaine for spinal anesthesia in C-section. *Anesth Analg* 1993; **77**: 457–62

11 Burm AG, Van Cleef JW, Gladines MP, Van Duinen M, Spierdjik J. Spinal anesthesia with hyperbaric lidocaine and bupivacaine: effects of epinephrine on plasma concentration profiles. *Anesth Analg* 1987; **66**: 1104–8

12 Collins JG, Kitahata LM, Matsumoto M, Homma E, Suzukawa M. Spinally administered epinephrine suppresses noxiously evoked activity of WDR neurons in the dorsal horn of the spinal cord. *Anesthesiology* 1984; **60**: 269–75

13 Gautier PE, Debry F, Fanard L, Van Steenberge A, Hody JL. Ambulatory combined spinal–epidural analgesia for labor. Influence of epinephrine on bupivacaine–sufentanil combination. *Reg Anesth* 1997; **22**: 143–9

14 Mercier FJ, Dounas M, Bouaziz H *et al.* The effect of adding a minidose of clonidine to intrathecal sufentanil for labor analgesia. *Anesthesiology* 1998; **89**: 594–601

15 D'Angelo R, Evans E, Dean LA, Gaver R, Eisenach JC. Spinal clonidine prolongs labor analgesia from spinal sufentanil and bupivacaine. *Anesth Analg* 1999; **88**: 573–6

16 Sia ATH. Optimal dose of intrathecal clonidine added to sufentanil plus bupivacaine for labour analgesia. *Can J Anesth* 2000; **47**: 875–80

17 Chiari A, Lorber C, Eisenach JC *et al.* Analgesic and hemodynamic effects of intrathecal clonidine as sole analgesic agent during first stage of labor. A dose response study. *Anesthesiology* 1999; **91**: 388–96

British Journal of Anaesthesia 89 (4). 567–70 (2002)

Remifentanil compared with sufentanil during extra-corporeal shock wave lithotripsy with spontaneous ventilation: a double-blind, randomized study

H. Beloeil[1], G. Corsia[1], P. Coriat[1] and B. Riou[1] [2]*

[1]Department of Anaesthesiology and Critical Care and [2]Department of Emergency Medicine and Surgery, Groupe hospitalier Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris (AP-HP), Université Pierre et Marie Curie, Paris, France

**Corresponding author: Département d'Anesthésie-Réanimation, Groupe hospitalier Pitié-Salpêtrière, 47 Boulevard de l'Hôpital, F-75651 Paris cedex 13, France*

Background. The pharmacokinetic properties of remifentanil may allow a rapid analgesic action during painful procedures and short lasting postoperative respiratory depression.

Methods. We carried out a randomized, blind, study in 60 patients to compare remifentanil (continuous i.v. infusion starting at 0.025 $\mu g\ kg^{-1}\ min^{-1}$) and sufentanil (i.v. doses of 0.15 $\mu g\ kg^{-1}$) during extra-corporeal shock wave lithotripsy (ESWL). Pain was assessed using a numerical pain scale (0–100), and pain relief was defined as a score $\leq$30. Respiratory depression was defined as a ventilatory frequency less than 10 breaths min^{-1} on two occasions or a peripheral oxygen saturation $\leq$92%, or administration of naloxone.

Results. The quality of analgesia was similar in both groups, during and after ESWL. During ESWL, there was no significant difference in respiratory depression in the remifentanil and sufentanil groups (53 vs 73%, NS). The percentage of satisfied patients (73 vs 83%, NS) and satisfied surgeons (97 vs 100%, NS) did not significantly differ between groups. After the procedure patients given remifentanil had less respiratory depression (20 vs 53%, $P<0.05$) and less nausea and vomiting (3 vs 20%, $P<0.05$).

Conclusion. A continuous i.v. infusion of remifentanil provided comparable analgesia and caused less respiratory depression and nausea and vomiting than i.v. boluses of sufentanil in patients undergoing extra-corporeal shock wave lithotripsy.

Br J Anaesth 2002; **89**: 567–70

Keywords: analgesics opioid, remifentanil; analgesics opioid, sufentanil; complications, respiratory depression; recovery, postoperative; ventilation, spontaneous

Accepted for publication: May 8, 2002

Extra-corporeal shock wave lithotripsy (ESWL) is a non-invasive procedure that allows urinary stones to be broken using acoustic shock waves. The impact of the shock waves causes transient stinging pain at the entry site and deep visceral discomfort, requiring analgesia during the procedure, usually by giving doses of sufentanil to spontaneously breathing patients. Respiratory depression during the procedure is treated with oxygen supplementation and verbal stimulation. After ESWL, patients no longer have pain but respiratory depression from the opioid can persist, requiring a stay in the postanaesthesia care unit (PACU), which can be long, depending on the amount of opioid given.

Remifentanil is a new opioid with short elimination half-life,[1 2] whose duration of action does not increase with increasing duration of administration because of rapid clearance and lack of drug accumulation.[1 3] These properties suggest that it may be particularly useful for ESWL with a rapid analgesic action during the painful procedure, and a very short duration of postoperative respiratory depression

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

that could reduce the duration of stay in the PACU. We performed a double-blind randomized study to compare sufentanil and remifentanil during ESWL. The primary end-point was the occurrence of respiratory depression in PACU. The quality of analgesia during the ESWL was the secondary end-point.

Methods

Patient selection

After institutional review board approval, written informed consent was requested during the anaesthesia consultation, which was performed at least 48 h before ESWL. During this consultation, the assessment of pain was explained to the patient. Patients were asked to rate their pain on a scale from 0 (no pain) to 100 (worst possible). The criteria of inclusion were: patients undergoing only ESWL, American Society of Anesthesiologists' (ASA) physical status I or II, and understanding of the pain score. We excluded patients if they were aged under 18 or had a major disability, a contraindication for using or allergy to opioids, severe chronic respiratory disease, a body mass index more than 35 kg m^{-2}, tetraplegia or paraplegia, or if the surgery was emergency or involved other procedures such as installing a ureteric tube at the same time.

Study design

Oral premedication with hydroxizine (100 mg) was given 1 h before ESWL. Just before entering the operating room, the patients were randomly assigned to one of the two treatment groups: remifentanil or sufentanil by opening a sealed envelope. During ESWL, patients blindly received one of the two analgesic treatments. In the sufentanil group, i.v. doses of sufentanil (0.15 $\mu g\ kg^{-1}$) were given as long as the reported pain score was greater than 30. A period of more than 5 min between two boluses was required. In the remifentanil group, remifentanil infusion (0.025 $\mu g\ kg^{-1}\ min^{-1}$) was given approximately 1 or 2 min before ESWL. The infusion rate was increased in steps of 0.025 $\mu g\ kg^{-1}\ min^{-1}$ each time the reported pain score was greater than 30. A period of more than 5 min between two steps was required. To ensure appropriate blinding, in the remifentanil group, patients received i.v. boluses of saline and a remifentanil infusion, whereas, in the sufentanil group, patients received a continuous infusion of saline and i.v. boluses of sufentanil. Moreover, when required, an i.v. bolus was given at the same time as the continuous i.v. infusion was increased. An anaesthetic nurse who did not take part in the care or the assessment of the patient prepared the solutions of the continuous infusion and boluses.

During ESWL, heart rate, arterial pressure, ventilatory frequency, peripheral oxygen saturation, and assessment of pain were recorded every 5 min. The level of energy of the ESWL shocks was decreased if pain was too severe. The same series of measurements were recorded every 10 min during the PACU period. Patients stayed at least 1 h in the PACU. After 1 h, patients left the PACU when the anaesthesiologist had assessed complete recovery with the modified Aldrete score.[4]

Study measurements

The primary end-point was the occurrence of a respiratory depression in the PACU. The respiratory depression was defined as a ventilatory frequency less than 10 breaths min^{-1} recorded at least two times (either in successive observations or not), or oxygen saturation ≤92%, or administration of naloxone given to treat severe respiratory depression (subjective clinical assessment by the anaesthesiologist). Oxygen supplementation (5 litre min^{-1}) was given during ESWL but not in the PACU, unless oxygen saturation was ≤92%. Respiratory depression during ESWL was also assessed using the same definition.

Secondary end-points were the quality of intraoperative analgesia, and any adverse effects of opioids. Patients were asked to verbally rate their level of pain (by using a pain rating score on a 1–100 scale) every 10 min throughout the procedure. Global patient satisfaction was scored on a three-point scale (completely satisfied, incompletely satisfied, and not satisfied) at the end of the procedure. Patients were recorded as satisfied only if they stated 'completely satisfied'. The surgeon completed a similar assessment at the end of the procedure. The maximum energy level of the ESWL, the duration of the procedure, and the need to decrease the energy level because of patient pain were also noted. We also noted: duration of stay in PACU, adverse effects of opioids during the intraoperative and PACU periods (pruritus, nausea and vomiting, sedation, vertigo, chest rigidity defined as difficulty to breathe normally using subjective assessment by the patient, and urinary retention), heart rate, arterial pressure, oxygen saturation, and ventilatory frequency.

Statistical analysis

Data are expressed as mean (SD) or median (extremes) for non-Gaussian variables, and numbers (percentages). Comparison of two means was performed using Student's *t*-test. Comparison of two medians was performed using the Mann–Whitney test. Comparison of two percentages was performed using Fisher's exact method. As most patients had low values for pain, neither the mean nor the median could appropriately describe the variable. Thus, only the number of patients with pain relief (score ≤30) were used for comparison between groups.

In a preliminary study of 20 consecutive patients given sufentanil, we observed that respiratory depression in the PACU occurred in 50% of cases. Thus, assuming α=0.05, β=0.10, and a reduction of the incidence of respiratory depression in the PACU from 50 to 10% with remifentanil, we calculated that at least 50 patients should be included.[5] Randomization was done with a random number table. All P values are two-tailed and a P value of <0.05 was considered significant. Statistical analysis was performed on a computer using NCSS 6.0 software (Statistical Solutions Inc., Cork, Ireland).

Results

Patient characteristics were not obviously different in the two groups (Table 1). The total dose of remifentanil was 221 (139) μg (range 47–625 μg) and the total dose of sufentanil 18 (7) μg (range 10–40 μg). During ESWL, there was no significant difference in the incidence of respiratory depression (53 *vs* 73%, NS) between the groups. Similarly, there was no significant difference in the quality of analgesia provided in the two groups (Fig. 1A). Only four patients reported some difficulty in breathing, but these difficulties were of moderate intensity and all patients find it acceptable. There were no significant differences between the two groups.

Table 1 Characteristic of the patients Data are mean (SD), [range], median {extremes} or number

	Sufentanil (n=30)	Remifentanil (n=30)
Age (yr)	46 (15) [23–73]	51 (17) [19–82]
Height (cm)	171 (7)	170 (8)
Weight (kg)	76 (15)	74 (14)
Body mass index (kg m^{-2})	25.8 (3.8)	25.8 (4.3)
Sex		
male	22	22
female	8	8
Indication of ESWL		
ureteral lithiasis	14	12
calix lithiasis	16	18
Position during ESWL		
supine	27	26
prone	3	4
Duration of ESWL (min)	34 {15–60}	35 {15–110}
Maximum ESWL energy (kJ)	18 (1)	17 (1)
Lowering of ESWL energy	13 (43)	10 (33)

In the PACU, patients given remifentanil had less respiratory depression, nausea and vomiting, than those given sufentanil (Table 2). No patient required naloxone. There was no significant difference in the quality of postoperative analgesia (Fig. 1B). There were no significant differences in the percentages of satisfied patients (73 *vs* 83%, NS) and satisfied surgeons (97 *vs* 100%, NS).

Discussion

Remifentanil and sufentanil were equally effective in providing analgesia and patient and surgeon satisfaction during ESWL, but remifentanil caused less respiratory depression and was associated with a lower incidence of nausea and vomiting, compared with sufentanil.

Remifentanil given along with propofol has been studied in patients spontaneously breathing via a laryngeal mask.[6 7] These studies showed that the remifentanil doses required for general anaesthesia under propofol are not compatible

Table 2 Opioid-related adverse effects Data are number $^{*}P<0.05$ *vs* sufentanil group †No patient required naloxone Sp_{O_2}, peripheral oxygen saturation

	Sufentanil (n=30)	remifentanil (n=30)
Pruritus	2	2
Nausea and vomiting	6	1*
Vertigo	3	2
Urinary retention	0	0
Chest rigidity	1	3
Postoperative respiratory depression†		
Sp_{O_2} ≤92%	7	2
ventilatory frequency <10 min^{-1}	12	4
both	3	0
total	16	6*

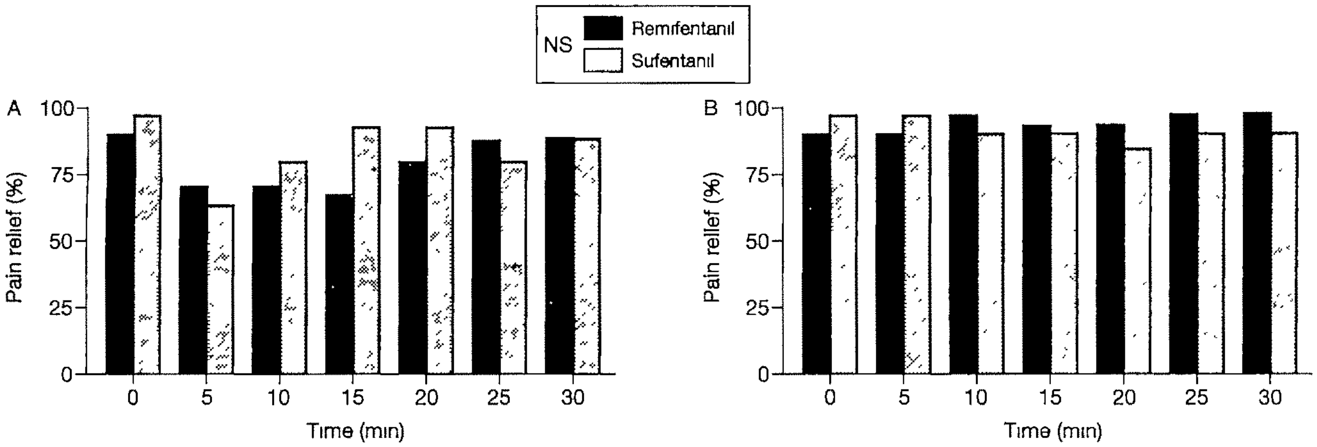


Fig 1 Percentage of patients with pain relief (defined as a reported pain score ≤30) in the remifentanil (n=30) and sufentanil groups (n=30) during ESWL (A) and in the PACU (B) Analysis during ESWL was limited to the first 30 min because the median duration was only 30 min.

with spontaneous ventilation. A technique with ventilation is more appropriate with this potent combination of respiratory depressant drugs. Only a few studies have used remifentanil alone in spontaneously breathing patients. Getsztesi and colleagues[8] compared remifentanil with other opioids during ESWL in spontaneously breathing patients without any airway protection and showed that more patients had low respiratory frequencies with remifentanil, but they obtained analgesia without any major respiratory depression. However, propofol was also given in this study.[8] In the same way, remifentanil provided adequate analgesia for ambulatory surgery without any respiratory depression at a dose of 1 $\mu g\ kg^{-1}$ followed by a continuous infusion of 0.1 $\mu g\ kg^{-1}\ min^{-1}$.[9] However, in this study an injection of local anaesthetic was required to perform the surgery.[9] To our knowledge, remifentanil has never been studied previously as a single agent for spontaneously breathing patients. Moreover, the manufacturer does not recommend using remifentanil during spontaneous ventilation. In healthy volunteers, remifentanil reduced the slope of the ventilatory response to carbon dioxide and the maximum ventilatory depression occurs 2.5 min after a single loading dose of 0.5 $\mu g\ kg^{-1}$.[10] The onset of respiratory depression appears to be more rapid than the onset of remifentanil-induced electroencephalographic slowing,[11] so patients could be apnoeic but awake. In our study, we started the infusion of remifentanil 1 or 2 min before ESWL, so the peak effect of drug on ventilation and pain coincided with the stimulation of surgery, and this probably limited the occurrence of respiratory depression. Premedication with hydroxizine may have also contributed to the moderate respiratory depression observed in our study.

Compared with previous studies, we used lower doses of remifentanil (0.025 $\mu g\ kg^{-1}$), which provided adequate analgesia for ESWL, which is not a very painful procedure. The doses allowed the prevention of intraoperative respiratory depression. Moreover, ESWL is not painful postoperatively. Remifentanil is the ideal opioid for this because its short half-life avoids adverse effects, including respiratory depression after the procedure time. The quality of analgesia provided was satisfactory for the patients and the surgeons. Less nausea and vomiting seen with remifentanil (Table 2) have not been described before to our knowledge, this is a clear advantage.

A potential shortcoming of our study is that we did not determine the ventilatory response to oxygen and carbon dioxide unlike Babenco and colleagues[10] in their study in healthy volunteers. We chose ESWL, because even if it is only mildly painful, it is an interesting 'model' of surgery, which is only painful during the intraoperative period. In fact, a modern system of ESWL installed in our hospital is not painful and no analgesia is now required. Nevertheless, the doses needed to obtain pain relief in our study were not negligible: 10–40 μg for sufentanil and 47–625 μg for remifentanil. Remifentanil has been recently advocated for short procedures such as minor gynaecological surgery,[11] prostatic and vesical biopsies,[12] breast biopsies,[13] and coronary percutaneous revascularization.[14] Although, we did not observe any severe adverse events, the power of our study to detect these is severely limited by the small sample and larger studies are needed to establish safety.

In summary, we found that, remifentanil used in equianalgesic doses caused less respiratory depression after the procedure than sufentanil when used for ESWL. We suggest that remifentanil is useful for this type of surgery (not painful after the procedure) and will reduce or even avoid stay in the PACU.

References

1 Glass PS, Hardman D, Kamiyama Y, *et al.* Preliminary pharmacokinetics and pharmacodynamics of an ultra-short-acting opioid: remifentanil. *Anesth Analg* 1993; **77**: 1031–40

2 Kapila A, Glass PSA, Jacobs JR, *et al.* Measured context-sensitive half-times of remifentanil and alfentanil. *Anesthesiology* 1995; **83**: 968–75

3 Westmoreland CL, Hoke JF, Sebel PS, Hug CC, Muir KT. Pharmacokinetics of remifentanil and its major metabolite in patients undergoing elective inpatient surgery. *Anesthesiology* 1993; **79**: 893–903

4 Aldrete JA, Kroulik D. A postanesthetic recovery score. *Anesth Analg* 1970; **49**: 924–34.

5 Casagrande JT, Pike MC. An improved approximate formula for calculating sample sizes for comparing two binomial distributions. *Biometrics* 1978; **34** 483–6

6 Peacock JE, Luntley JB, O'Connor B, *et al.* Remifentanil in combination with propofol for spontaneous ventilation anaesthesia. *Br J Anaesth* 1998; **80**: 509–11

7 Murdoch JA, Hyde RA, Kenny GN. Target-controlled remifentanil in combination with propofol for spontaneously breathing day-case patients. *Anaesthesia* 1999; **54**: 1028–31

8 Gesztesi Z, Sa Rego M, White PF. The comparative effetiveness of fentanyl and its newer analogs during extracorporeal shock wave lithotripsy under monitored anesthesia care. *Anesth Analg* 2000, **90**: 567–70

9 Gold MI, Watkins D, Sung YF, *et al.* Remifentanil versus remifentanil/midazolam for ambulatory surgery during monitored anesthesia care. *Anesthesiology* 1997; **87**: 51–7

10 Babenco HD, Conard PF, Gross JB. The pharmacodynamic effect of a remifentanil bolus on ventilatory control. *Anesthesiology* 2000; **92** 393–8

11 Egan TD, Minto CF, Hermann DJ, Barr J, Muir KT, Shafer SL. Remifentanil versus alfentanil: comparative pharmacokinetics and pharmacodynamics in healthy adult male volunteers. *Anesthesiology* 1996; **84**: 821–33

12 Tablov V, Tablov B, Partenov P. Analgesia with remifentanil or remifentanil/midazolam for minor gynaecological surgery: efficacy and patient comfort. *Eur J Anaesthesiol* 2001; **18** (Suppl 21): 14(Abstract)

13 Drogheti L, Zopellari R, Morghen I, Forni E. Remifentanil in pump vs. alfentanil in bolus in outpatient anaesthesia. *Eur J Anaesthesiol* 2001; **18** (Suppl 21): 14(Abstract)

14 Unlugenç H, Ozalevli M, Guler T, Isık G Comparison of different dosages of remifentanil administration during brief painful procedures. *Eur J Anaesthesiol* 2001; **18** (Suppl 21): 15(Abstract)

15 Robert A, Forestier F, Soubiron L, Domblides N, Janvier G. Conscious sedation with remifentanil during coronary atherectomy. *Eur J Anaesthesiol* 2001; **18** (Suppl 21): 90(Abstract)

British Journal of Anaesthesia **89** (4): 571–9 (2002)

Phenotyping malignant hyperthermia susceptibility by measuring halothane-induced changes in myoplasmic calcium concentration in cultured human skeletal muscle cells

T. Girard[1]*, S. Treves[1], K. Censier[1], C. R. Mueller[2], F. Zorzato[1 3] and A. Urwyler[1]

[1]Departments of Anaesthesiology and Research, Kantonsspital/University of Basel, CH-4031 Basel, Switzerland. [2]Institut fuer Humangenetik, Biozentrum, University of Wuerzburg, D-97074 Wuerzburg, Germany. [3]Department of Experimental and Diagnostic Medicine, General Pathology Section, University of Ferrara, Via Borsari 46, I-44100 Ferrara, Italy.

**Corresponding author*

Background. Malignant hyperthermia (MH) is a potentially lethal disease triggered by volatile anaesthetics and succinylcholine in genetically predisposed individuals. Because of the heterogenetic nature of MH, a simple genetic-based diagnostic test is not feasible and diagnosis requires an invasive open muscle biopsy followed by the *in vitro* contracture test (IVCT). Our aim was to establish if measurements of halothane-induced increases in intracellular calcium ion concentration $[Ca^{2+}]_i$ in cultured human skeletal muscle cells can be used to phenotype MH susceptibility and if different mutations in the ryanodine receptor (RYR1) gene affect halothane-induced increases in $[Ca^{2+}]_i$.

Methods. Primary cultures of human skeletal muscle cells were established from 54 individuals diagnosed by the IVCT according to the protocol of the European MH Group as: MH susceptible (*n*=22), MH negative (*n*=18) or MH equivocal (*n*=14). All individuals were screened for the presence of the most common mutations in the RYR1 gene. $[Ca^{2+}]_i$ was measured by fluorescent digital microscopy using fura-2/AM in 10 cells from each patient at five different halothane concentrations.

Results. The halothane-induced increase in $[Ca^{2+}]_i$ differed significantly between the three diagnostic groups. Different mutations of the RYR1 gene did not have a specific impact on halothane-induced increases in $[Ca^{2+}]_i$.

Conclusions. Measurements of $[Ca^{2+}]_i$ in human skeletal muscle cells can be used to phenotype MH susceptibility; however, we did not observe a specific effect of any mutation in the RYR1 gene on the halothane-induced increase in $[Ca^{2+}]_i$.

Br J Anaesth 2002; **89**: 571–9

Keywords: anaesthesia; anaesthetics volatile, halothane; ions, calcium; muscle, skeletal, myoblasts

Accepted for publication: June 11, 2002

Malignant hyperthermia (MH) is a pharmacogenetic disease triggered by halogenated anaesthetics and succinylcholine in predisposed individuals.[1–3] The incidence of MH episodes is about 1 in 15 000 anaesthetics in children and 1 in 50 000 in adults, although these figures may underestimate the true prevalence, since many reactions occur in patients who have previously come into contact with trigger agents and had uneventful anaesthesia.[4 5] Symptoms characterizing an impending MH crisis include a rapid and sustained increase in body temperature, skeletal muscle rigidity, acidosis, rhabdomyolysis and tachycardia[6] or any combination of the above (see review by Gronert and colleagues[3]). If such a reaction is not recognized in its early phases and treatment quickly initiated, the patient is likely to die.

In their daily lives MH-predisposition does not pose a threat to MH-susceptible (MHS) individuals, so the major goal of MH diagnostics is to identify susceptible individuals before the administration of trigger agents.[7 8] To date the gold standard of MH diagnosis is the *in vitro* contracture test (IVCT). This invasive procedure involves an open muscle biopsy and *in vitro* challenge of muscle strips with halothane or caffeine. According to the guidelines of the

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Table 1 Family of origin (a capital letter indicates members belonging to the same family, the absence of a letter indicates single members of a family), identification of malignant hyperthermia (MH)-linked ryanodine receptor (RYR1) mutation and *in vitro* contracture test (IVCT) of muscle biopsies. MHN=MH negative; MHS=MH susceptible, MHE=MH equivocal

				IVCT – halothane		IVCT – caffeine	
Number	**Status**	**Family**	**RYR1 mutation**	**Threshold (%)**	**Contracture (g) at 2%**	**Threshold (mM)**	**Contracture (g) at 2 mM**
1	MHN	A		>3	0.05	>4	0
2	MHN	A		>3	0.15	4	0
3	MHN	A		>3	0.05	>4	0
4	MHN	B		3	0.15	>4	0.1
5	MHN	C		>3	0.1	>4	0.1
6	MHN	C		3	0.15	4	0
7	MHN	D		>3	0.15	>4	0
8	MHN	D		3	0.1	4	0
9	MHN	D		>3	0.05	>4	0
10	MHN	D		>3	0.05	>4	0.05
11	MHN	D		>3	0.05	>4	0.05
12	MHN	D		>3	0.05	>4	0.05
13	MHN			>3	0.1	4	0
14	MHN			>3	0.05	>4	0
15	MHN			>3	0.1	>4	0.1
16	MHN			>3	0.1	>4	0
17	MHN			>3	0	4	0.1
18	MHN			>3	0.05	4	0.05
1	MHE	A	Arg614Cys	1	0.85	3	0
2	MHE	A		1	1.15	4	0.05
3	MHE	B		2	0.35	4	0.05
4	MHE	B		1	0.4	4	0.1
5	MHE	C		1	1.7	3	0
6	MHE	D		2	0.3	4	0
7	MHE	E		1	0.7	4	0
8	MHE	E		1	1	3	0.05
9	MHE			2	0.3	>4	0.1
10	MHE			0.5	1.3	3	0.1
11	MHE			2	0.3	>4	0.05
12	MHE			1	1.35	3	0.05
13	MHE			2	0.4	4	0.05
14	MHE			1	0.85	3	0.05
1	MHS	A	Arg614Cys	0.5	5.1	0.5	2.7
2	MHS	B	Gly2434Arg	0.5	1.3	2	0.25
3	MHS	C	Val2168Met	0.5	5.1	1.5	1.2
4	MHS	C	Val2168Met	0.5	4.6	1.5	2.7
5	MHS	C	Val2168Met	0.5	4.5	1	2.35
6	MHS	C	Val2168Met	0.5	2.1	1.5	1.35
7	MHS	D	Val2168Met	0.5	3.75	1	1.45
8	MHS	D	Val2168Met	0.5	2.65	1	1.65
9	MHS	E		0.5	3.9	1	1.9
10	MHS	F	Val2168Met	1	1.45	2	0.2
11	MHS	F	Val2168Met	0.5	3.55	1	2.25
12	MHS	G		0.5	3.5	1.5	0.4
13	MHS	G		0.5	3.05	1.5	0.65
14	MHS	G		1	1.6	0.5	1.6
15	MHS	G		0.5	2.6	1	1.3
16	MHS		Val2168Met	0.5	1.8	2	0.8
17	MHS		Arg2458Cys	0.5	1	1.5	0.7
18	MHS			1	2	1.5	0.4
19	MHS			0.5	1.95	1	1.3
20	MHS		Val2168Met	0.5	1.7	1.5	0.7
21	MHS		Val2168Met	1	1.05	1	1.3
22	MHS			1	0.9	2	0.25

European MH Group, patients are then diagnosed as MHS or MH negative (MHN) on the basis of contractile threshold and sensitivity of the muscle bundles to halothane and caffeine. If contracture is achieved only with either caffeine or halothane, the patient is diagnosed as MH equivocal (MHE).[6 9]

The underlying cause of MH is an abnormality in skeletal muscle calcium metabolism.[10 11] Therefore, alterations in proteins involved in the regulation of the intracellular calcium concentration ($[Ca^{2+}]_i$), such as the calcium pump, the calcium release channel or other proteins implicated in excitation–contraction coupling, could potentially cause

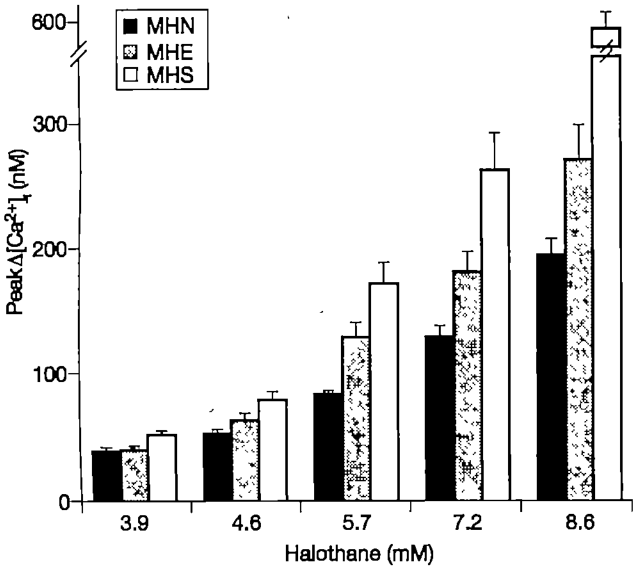


Fig 1 Average peak change (Δ) in $[Ca^{2+}]_i$ induced by different halothane concentrations in human skeletal muscle cells. Single-cell intracellular calcium measurements were performed with the fluorescent calcium indicator fura-2/AM, using a Zeiss imaging system attached to an Axiovert fluorescent microscope, as described in the Methods section Results are mean (SEM); the number of cells measured ranged between 132 and 246 for each halothane concentration and diagnostic group The halothane-induced increase in $[Ca^{2+}]_i$ was significantly different between the three diagnostic groups ($P<0.001$) and between the different halothane concentrations ($P<0.0001$; repeated measurements ANOVA) Fisher's PLSD post-hoc test revealed significant differences ($P<0.001$) between all halothane concentrations, with the exception of 3.9 *vs* 4.6 mM.

MH. Studies into the molecular mechanisms underlying this disease have demonstrated that the ryanodine receptor (RYR1) gene on human chromosome 19q is the primary locus of MH.[2 7 12] Mutation screening has identified more than 30 mutations in the RYR1 gene so far. Although approximately 50% of MH families have mutations in the RYR1 gene, linkage studies have revealed that this is a heterogenetic disease.[7 12–16]

The aim of the present study was to determine if halothane-induced increases in $[Ca^{2+}]_i$ in human skeletal muscle cells can be used to phenotype MH susceptibility and if different mutations in the RYR1 gene have a distinct effect on the halothane-induced increases in $[Ca^{2+}]_i$.

Methods

Study protocol

In order to determine if halothane-induced increases in $[Ca^{2+}]_i$ in human skeletal muscle cells can be used to phenotype MH susceptibility, we compared the results obtained by the IVCT with results obtained by measuring the halothane-induced increase in $[Ca^{2+}]_i$ in cultured skeletal muscle cells. Patients included in the study were tested by the IVCT according to the protocol of the European MH Group.[9] On the same day, primary skeletal muscle cell cultures were established from surplus fragments of the muscle biopsies. For each patient, increases in $[Ca^{2+}]_i$ were measured in 10 muscle cells after exposure to 3.9, 4.6, 5.7, 7.2 or 8.6 mM halothane. These concentrations were chosen because in a previous study[17] we found that the biggest differences in $[Ca^{2+}]_i$ between cells from MHS and MHN individuals were obtained in this range of halothane concentrations.

In order to determine if different mutations have a different effect on halothane-induced increases in $[Ca^{2+}]_i$, all patients were screened for nine of the most common mutations in the RYR1 gene (described below) and the increases in $[Ca^{2+}]_i$ in subjects carrying different mutations, as well as in subjects carrying the same mutation in the RYR1 gene, were analysed and compared.

Patient selection

We selected 54 patients from 26 families with a positive history of MH without clinical signs of neuromuscular disease. The age range of the patients was 8–59 yr. Twenty-two patients were diagnosed as MHS, 18 as MHN and 14 as MHE by IVCT. Patients were classified as MHS if a contracture force ⩾0.2 g was elicited by at least 2% halothane and 2 mM caffeine, as MHE if a contracture force ⩾0.2 g was elicited only by either caffeine or halothane, and MHN if contractures ⩾0.2 g were not reached with either trigger agent. The characteristics of the individuals involved in this study, including contractures obtained from the muscle strips during the IVCT, family of origin and mutation found are given in Table 1.

The protocol for the study was approved by the University of Basel Hospital Ethics Committee and written informed consent was obtained from patients.

Materials

Dulbecco modified Eagle (DME) medium containing 4.5 mg ml^{-1} glucose, fetal calf serum (FCS), horse serum, penicillin G and streptomycin was purchased from Life Technologies Ltd, Paisley, UK. Insulin was purchased from Eli Lilly and Co., Indianapolis, IN, USA. Cell culture material was from Becton Dickinson GmbH, Heidelberg, Germany. Halothane was from Halocarbon Labs, Inc, Hackensack, NJ, USA. The mammalian blood DNA isolation kit and Taq polymerase and DNA restriction enzymes were from Roche Molecular Biochemicals (Basel, Switzerland). The kit for DNA isolation from tissue was from Machery-Nagel GmbH, Duren, Germany The polymerase chain reaction (PCR) purification kit was from Qiagen GmbH, Hilden, Germany. Fura-2/AM and ionomycin were from Sigma Chemical Co., St Louis, MO, USA. Primers were from Microsynth GmbH, Balgach,

Table 2 Halothane-induced changes (Δ) in $[Ca^{2+}]_i$, 340/380 nm ratio and integral calcium in primary cultures derived from MHN individuals: definition of cut-off values

Halothane concentration (mM)	*n*	Percentile 50th	75th	90th	95th	97th
Δ $[Ca^{2+}]_i$						
3.9	198	31	50.6	85.1	110.3	117.2
4.6	198	47	74	101	127	137.9
5.7	205	72.7	105.5	167	203.5	230.6
7.2	178	106	158.6	239.2	310.4	507.2
8.6	173	139.5	265.6	391.4	513.8	570.5
Δ 340/380 nm ratio						
3.9	198	0.07	0.09	0.13	0.15	0.176
4.6	198	0.09	0.13	0.17	0.201	0.233
5.7	205	0.13	0.187	0.27	0.347	0.409
7.2	178	0.2	0.28	0.35	0.376	0.43
8.6	173	0.25	0.422	0.57	0.677	0.733
Integral calcium						
3.9	220	2.5	4.8	7.5	9.1	9.9
4.6	209	3.8	7.6	10.4	11.7	12.8
5.7	206	4.3	9.6	12	15.3	18.3
7.2	216	8.7	13.5	22	28.7	31.1
8.6	206	13.1	23.3	34.7	40.9	45.6

Table 3 Diagnosis of MH susceptibility by single-cell calcium measurements (changes in (Δ)$[Ca^{2+}]_i$, 340/380 nm ratio and integral calcium) compared with *in vitro* contracture test (IVCT)-based diagnosis. MHN=MH negative, MHS=MH susceptible, MHE=MH equivocal

	Diagnosis by IVCT MHN (*n*=18)	MHE (*n*=14)	MHS (*n*=22)
Δ $[Ca^{2+}]_i$ >95th percentile	1 (6%)	4 (29%)	15 (68%)
Δ $[Ca^{2+}]_i$ >97th percentile	0	2 (14%)	11 (50%)
Δ ratio >95th percentile	1 (6%)	5 (36%)	15 (68%)
Δ ratio >97th percentile	1 (6%)	4 (29%)	13 (59%)
Integral calcium >95th percentile	2 (11%)	7 (50%)	12 (55%)
Integral calcium >97th percentile	1 (6%)	5 (36%)	11 (50%)

Switzerland. All other chemicals were reagent grade or of highest available grade.

Human skeletal muscle cell cultures

Primary human muscle cell cultures were established from surplus fragments taken from biopsies of patients undergoing diagnostic IVCT as described previously.[17] Cells were grown in DME, 10% horse serum, insulin 5 ng ml^{-1}, 2 mM glutamine, antibiotics and 7 mM HEPES, pH 7.4 (proliferative medium) under standard cell culture conditions. For cryopreservation, about 10^6 cells were resuspended in DME containing 40% FCS and 10% DMSO and were stored in liquid nitrogen.

$[Ca^{2+}]_i$ measurements

For measurements of $[Ca^{2+}]_i$, cells were trypsinized and transferred from tissue culture flasks to glass coverslips and allowed to grow in proliferative medium until groups of cells were visible. We have previously demonstrated that under these culture conditions the cells acquire skeletal-muscle-specific proteins such as sarcomeric α-actinin and type-1 RYR,[17] although they do not fully differentiate into multinuclear myotubes. Such primary cultures exhibit a degree of variability in the maturity of individual cells.

Cells to be tested were loaded with the fluorescent calcium indicator fura-2/AM. Single-cell calcium measurements using fluorescence microscopy were performed on 10 cells before and after the addition of halothane. A new coverslip containing fura-2/AM-loaded cells was used for each halothane concentration. For each experiment a total of 72 digital images were recorded at excitations of 340 and 380 nm and the ratio calculated, as per our previous study.[17] The values obtained during the first 10 cells (i.e. before the application of halothane) were used to calculate the resting $[Ca^{2+}]_i$. Values were then taken during halothane perfusion as well as after addition of EGTA/ionomycin and calcium ions to obtain R_{min} (the value obtained in the presence of EGTA) and R_{max} (the value obtained in the presence of high

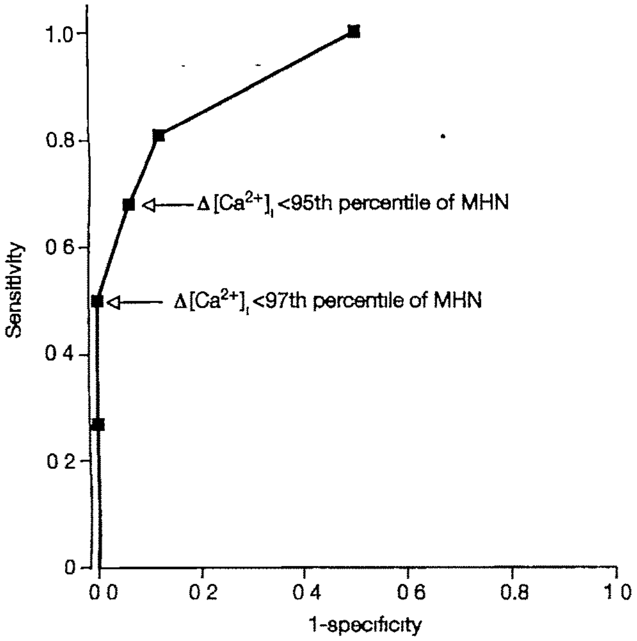


Fig 2 Receiver operating characteristic (ROC) curve comparing the diagnostic results of $[Ca^{2+}]_i$ measurements at different cut-off values (50–99th percentile) with IVCT diagnosis. The curve shows sensitivity and specificity of the $[Ca^{2+}]_i$ measurements for the diagnosis of MH susceptibility

calcium after the addition of ionomycin). Each run lasted approximately 6 min, including the time taken to run the calibration at the end of the experiment. Halothane in DMSO was administered at the indicated concentrations from a gas-tight vial by means of a roller pump. Its actual concentration was verified by gas chromatography in several test runs using fixed flow rates, temperature and tubing. Calibration was performed using the EGTA/ionomycin/manganese chloride method.[18] The changes in fluorescence were converted into $[Ca^{2+}]_i$ using the formula $[Ca^{2+}]_i=[k_D \times (R-R_{min})/(R_{max}-R)] \times Sf2/Sb2$, where k_D (dissociation constant) of fura-2/AM was assumed to be 225 nM and Sf2 and Sb2 are the fluorescent values for Ca^{2+} free (f) and bound (b) of the indicator. These values are a constant.

The ratios were analysed and converted into $[Ca^{2+}]_i$ values (nM) using a programmable database application (Omnis 7/3 from Blyth Holding Inc., Suffolk, UK). The increase in $[Ca^{2+}]_i$ was determined by the difference between resting $[Ca^{2+}]_i$ and peak $[Ca^{2+}]_i$ after the addition of halothane. The whole transient elicited by a given halothane concentration was used to calculate the integral calcium, which reflects the total amount of calcium released.

Mutation screening

Screening for the presence of nine of the most frequent MH-linked mutations (Arg163Cys, Gly341Arg, Arg614Cys, Arg614Leu, Arg2163Cys, Val2168Met, Gly2434Arg, Arg2458Cys, Arg2458His) was performed by genomic DNA PCR amplification followed by restriction enzyme digestion and polyacrylamide gel electrophoresis. Total genomic DNA was isolated from either peripheral blood or muscle fragments not used for IVCT. PCR conditions and primer sequences were as described previously.[19]

Statistical analysis

The $[Ca^{2+}]_i$ measurements from the three diagnostic groups were compared using repeated measurements ANOVA. Within each halothane concentration, the results from the three diagnostic groups were compared using Fishers's protected least significant difference (PLSD) post-hoc test.

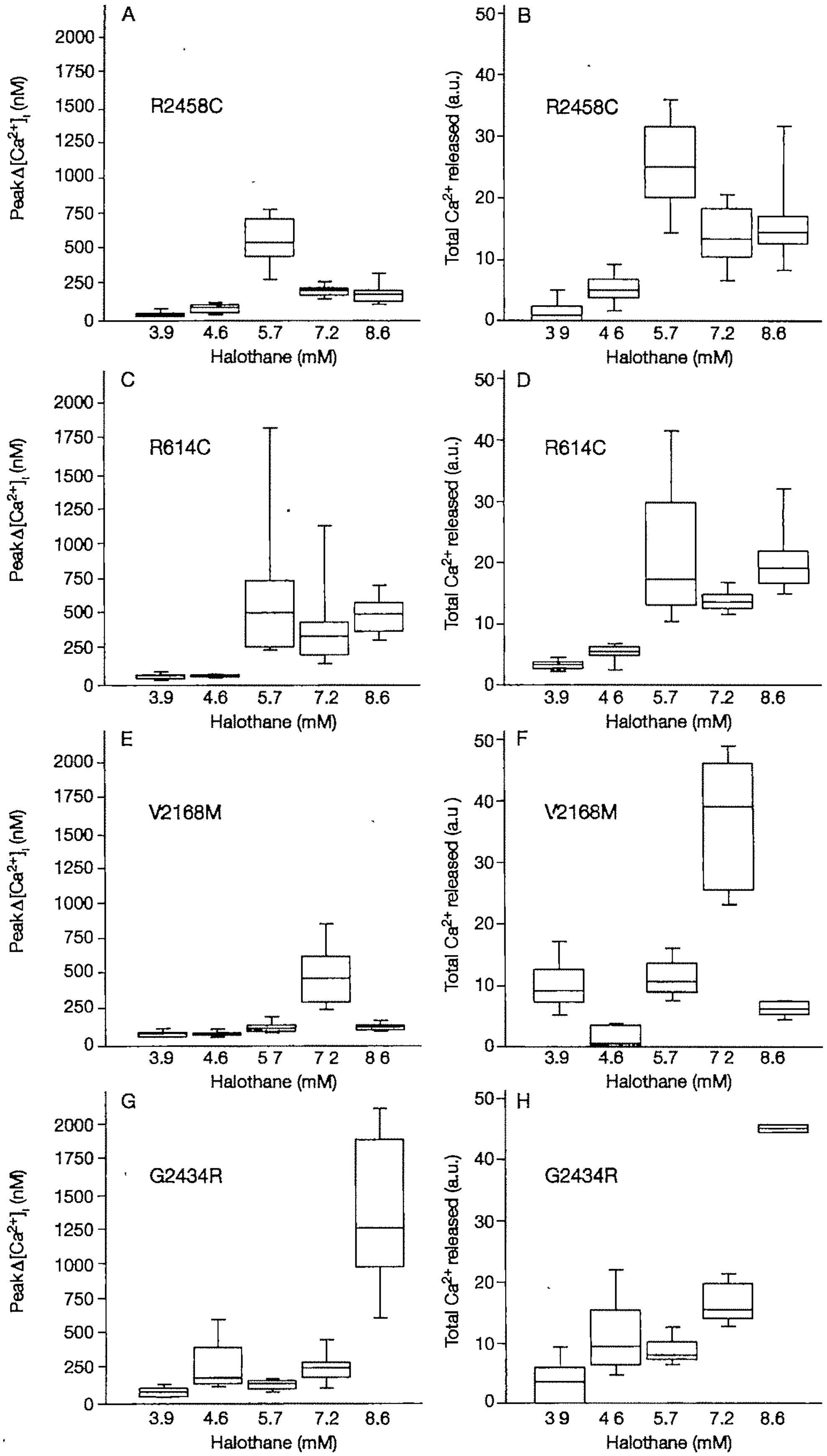
To determine normal $[Ca^{2+}]_i$ values, all measurements of the MHN cells were pooled and median values, as well as 75th, 90th, 95th, 97th and 99th percentiles, were calculated for each halothane concentration. These percentile values were used to define different cut-off values. Median values were calculated for each individual at the five halothane concentrations and compared with the cut-off values defined by the MHN population. If the cut-off value was exceeded at any concentration of halothane, the patient was classified as MHS.

StatView (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis.

Results

MH phenotyping by $[Ca^{2+}]_i$ measurements

We investigated intracellular calcium homeostasis in primary skeletal muscle cells obtained from 22 individuals diagnosed as MHS, 14 individuals diagnosed as MHE and 18 individuals diagnosed as MHN by IVCT, according to the European MH Group protocol. Single-cell $[Ca^{2+}]_i$ measurements were performed at the five halothane concentrations in 10 fura-2/AM-loaded cells, the fluorescent changes induced by halothane were converted into $[Ca^{2+}]_i$ values by performing signal calibration at the end of each experiment. Some cells contracted when high intracellular calcium concentrations were reached, so the fluorescence signal could not be calibrated. These cells were therefore excluded from Figure 1, in which we show the peak $[Ca^{2+}]_i$ induced by halothane. The results depicted in Figure 1 show that halothane-induced increases in $[Ca^{2+}]_i$ in primary skeletal muscle cells differed significantly between MHS, MHE and MHN individuals. The increases in $[Ca^{2+}]_i$ were dose dependent ($P<0.0001$; repeated measurements ANOVA; Figure 1). In addition, the increases in $[Ca^{2+}]_i$ in muscle cells from MHS and MHE individuals were shifted to lower halothane concentrations when compared with cells from MHN individuals ($P<0.0001$; repeated measurements ANOVA, Figure 1). Fisher's PLSD post-hoc test revealed significant differences ($P<0.001$) between all


A
R2458C
Peak Δ[Ca2+]i (nM)
0
250
500
750
1000
1250
1500
1750
2000
3.9
4.6
5.7
7.2
8.6
Halothane (mM)
B
R2458C
Total Ca2+ released (a.u.)
0
10
20
30
40
50
3.9
4.6
5.7
7.2
8.6
Halothane (mM)
C
R614C
Peak Δ[Ca2+]i (nM)
D
R614C
Total Ca2+ released (a.u.)
E
V2168M
Peak Δ[Ca2+]i (nM)
F
V2168M
Total Ca2+ released (a.u.)
G
G2434R
Peak Δ[Ca2+]i (nM)
H
G2434R
Total Ca2+ released (a.u.)

halothane concentrations, with the exception of 3.9 *vs* 4.6 mM.

Cut-off values for the determination of MH susceptibility by $[Ca^{2+}]_i$ measurements were calculated on the basis of results from the individuals diagnosed as MHN by the IVCT and are presented in Table 2. Using the 95th percentile as a cut-off value, MH susceptibility was diagnosed by measurements of $[Ca^{2+}]_i$ in 15 of 22 MHS patients (68%), 4 of 14 MHE patients (29%) and 1 of 18 MHN patients (6%) (Table 3). We calculated sensitivity and specificity by comparing results obtained by the $[Ca^{2+}]_i$ measurements with results obtained by the IVCT. Using the 95th percentile as a cut-off value, the specificity was 0.94 (95% confidence intervals [CI] 0.73 to 1.0, Table 3, Fig. 2) and the sensitivity was 0.68 (95% CI 0.45 to 0.86). Taking into account that the specificity of the IVCT using the European MH Group protocol is 0.93,[20] the actual number of MHS could be 20 instead of 22. This would increase the sensitivity of $[Ca^{2+}]_i$ measurements to 0.75 (95% CI 0.51 to 0.91).

Effect of RYR1 gene mutations on halothane-induced increases in $[Ca^{2+}]_i$

We next investigated whether the presence of different RYR1 gene mutations has an impact on halothane-induced $[Ca^{2+}]_i$ transients and whether cells from different patients carrying the same mutation respond in a similar way. Figure 3 shows a box plot of the halothane-induced $[Ca^{2+}]_i$ transients (peak $[Ca^{2+}]_i$ and total amount of $[Ca^{2+}]_i$ released) from individuals carrying four different MH-linked mutations. The increase in $[Ca^{2+}]_i$ is particularly evident at halothane concentrations ≥5.7 mM and was irrespective of the mutation.

The halothane 'trigger concentration' appears to vary between individuals with different mutations.[19,21] In order to study if this is specific for a given mutation or a more general phenomenon, we analysed the halothane-induced peak $[Ca^{2+}]_i$ in cells obtained from unrelated individuals carrying the same Val2168Met mutation. Halothane trigger concentrations and peak $[Ca^{2+}]_i$ were different in these unrelated individuals (Fig. 4), suggesting that the genetic background influences the halothane-induced increase in $[Ca^{2+}]_i$.

Discussion

In the present report we show that halothane-induced increases in $[Ca^{2+}]_i$ in human skeletal muscle cells can be used to phenotype MH susceptibility. However, our results show that different mutations in the RYR1 gene have no specific effect on halothane-induced increases in $[Ca^{2+}]_i$. Measurements of halothane-induced increases in $[Ca^{2+}]_i$ in human skeletal muscle cells confirmed the IVCT diagnosis of MH susceptibility in 15 of 22 MHS individuals (68%) when the 95th percentile of the values obtained from the MHN population was used as a cut-off value. Taking into account that the specificity of the IVCT following the protocol of the European MH Group is 0.93, this could reduce the number of MHS individuals to 20, leading to an increase in the number of coinciding MHS diagnoses (15 of 20, 75%). Only one MHN individual exceeded the 95th percentile cut-off value. This discordance could be due to either a wrong IVCT diagnosis or oversensitivity of diagnosis based on measurements of halothane-induced increases in $[Ca^{2+}]_i$.

In seven of 22 individuals the IVCT diagnosis of MHS could not be confirmed by halothane-induced increases in $[Ca^{2+}]_i$. This could be due to either a reduced specificity of the IVCT (not every MHS diagnosis can be confirmed by molecular genetic analysis), or to an overestimation of the halothane-induced increases in $[Ca^{2+}]_i$ of the true 'normal' population—in the present study 'normal' $[Ca^{2+}]_i$ values were obtained from individuals from MHS families, not from non-MH-linked individuals.

In this study we confirm and extend our previous results. In fact, our earlier work was based on observations carried out on two MHS subjects and three MHN subjects while in this study we also included 14 MHE individuals, and the number of patients involved was 10 times larger. In the study by Censier and colleagues,[17] we observed that the maximum difference between MHS and MHN, as far as halothane-induced increases in $[Ca^{2+}]_i$ are concerned, occurred at halothane concentrations of 5.7–9.5 mM. In addition, we confirm that the mean increase in $[Ca^{2+}]_i$ of cells from MHN individuals occurring at 8.6 mM halothane is similar to that of cells from MHS individuals at 5.7 mM halothane (203 nM *vs* 167 nM, respectively; P=0.269, student's *t*-test for unpaired samples).

The response of cells presented in our previous report[17] seem to be different from those found in this study. In the present study we examined a larger sample than previously and we believe that the values obtained are more likely to represent the MHN population. We would like to point out that it is very important to perform $[Ca^{2+}]_i$ measurements at several halothane concentrations and we suggest concentrations ranging around 5.7 mM since this is the concentration where maximal differences can be observed.

Fig 3 Halothane-induced $[Ca^{2+}]_i$ response of cultured human skeletal muscle cells for four individuals Single-cell $[Ca^{2+}]_i$ measurements were performed as described in Figure 1. The box plot shows median peak Δ $[Ca^{2+}]_i$ and median total calcium release induced at each halothane concentration, together with 10th, 25th, 75th and 90th percentiles. Panels A, C, E and G show the peak $[Ca^{2+}]_i$, panels B, D, F and H show total amount of calcium released (arbitrary units, a.u.) by halothane in individuals carrying the indicated RYR1 mutation. Mutation screening was performed as described in the Methods section

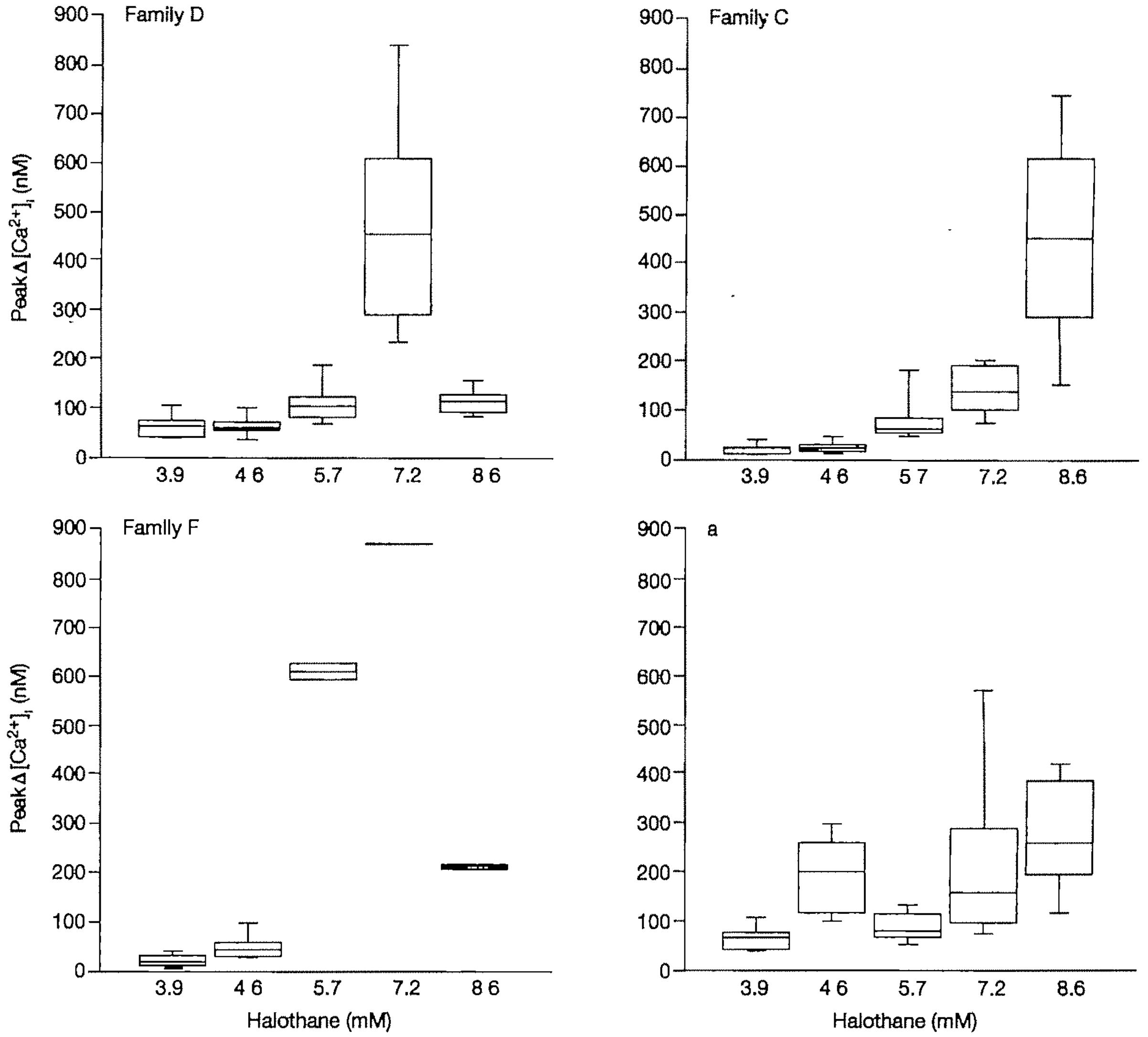


Fig 4 Halothane-induced [Ca^{2+}]$_i$ response of cultured human skeletal muscle cells from single members of four families carrying the same Val2168Met mutation (families D, C and F – as given in Table 1; the individual shown in panel a was the only member of this family investigated). Median peak Δ [Ca^{2+}]$_i$ induced by each halothane concentration, together with 10th, 25th, 50th, 75th and 90th percentile are shown in the box plot. Conditions are described in the legend to Figure 1

In this study we used small fragments of tissue (2–4 mm^3) left over from muscle biopsies. We have already assessed the feasibility of obtaining primary cultures from needle biopsies (unpublished observations). This approach offers obvious physical advantages for the patients, as well as being cheaper. Obviously there are some limitations in the use of this novel approach: (i) the need for cell culture and fluorescent calcium imaging facilities, (ii) the fact that cells cultured from the biopsies give rise to heterogeneous cell populations that do not respond to halothane in a uniform way, (iii) not all individuals diagnosed as MHS by IVCT had an halothane-induced increase in [Ca^{2+}]$_i$ beyond that of the MHN population.

As to the future of MH diagnostics, one can envisage that individuals from families with defined mutations could first undergo genetic testing.[22] If no mutation is found, they could undergo a skeletal muscle needle biopsy followed by measurements of halothane-induced increases in [Ca^{2+}]$_i$. If measurements of [Ca^{2+}]$_i$ do not reveal MH susceptibility, then an IVCT could be performed. With this less invasive and stepwise approach, the high sensitivity of the IVCT and thus the high safety level of MH diagnostics is maintained. In fact if these criteria were used, only three of the 22 MHS individuals and seven of the 14 MHE individuals would still require the invasive IVCT. For the time being, however, all the MHN individuals would still require IVCT testing.

The common final pathway for MH is the loss of the fine regulation of calcium homeostasis in muscle cells. The present investigation is not only potentially important from a clinical point of view, but also from a biological one. In fact, it indicates that although a variety of factors such as metabolic processes, muscle training, protein composition and enzyme activation may influence the IVCT (at least as far as contracture force is concerned), there is an intrinsic 'defect' in the machinery involved in $[Ca^{2+}]_i$ homeostasis in MHS individuals. Each individual may compensate for the molecular defect in a variety of ways, which may be influenced by the specific mutation present as well as other genetic and 'environmental' factors. This hypothesis is supported by the fact that the halothane-induced changes in $[Ca^{2+}]_i$ in cells from MHS individuals bearing the same point mutation but with a different genetic background do not coincide, and because MHS individuals with RYR1 mutations do not undergo MHS reactions at every contact with trigger agents.[4,5] Our results also show that the penetrance of a given mutation varies between individuals. This observation would be expected in view of the fact that the RYR must assemble as a tetramer in order to function as a calcium channel. The results of this study, as well as data from IVCT, tend to favour the hypothesis that mutated channels are probably randomly distributed, giving rise to 'heterogeneous' responses, but the presence of a single mutated channel is sufficient to confer the MHS phenotype. This hypothesis is supported by our previous work,[17] in which the normal phenotype was not reconstituted by transfecting MHS cells with wild-type channels.

In conclusion, measurements of $[Ca^{2+}]_i$ may be useful in increasing the accuracy of MH phenotyping and may therefore be used as a complementary method for the diagnosis of MH susceptibility.

Acknowledgements

We would like to thank Esther Schmid for performing the cell cultures. This work was supported by Swiss National Foundation grant number 32-47176 96 and by a grant by the Swiss Foundation for Neuromuscular Research and from the Department of Anaesthesia, University Hospital Kantonsspital Basel.

References

1 Denborough M. Anaesthetic deaths in a family. *Lancet* 1960; **2**· 45

2 Denborough M. Malignant hyperthermia. *Lancet* 1998; **352**: 1131–6

3 Gronert G, Antonigni J, Pessah I. Malignant hyperthermia. In: Miller R, ed. *Anesthesia*. New York. Churchill Livingstone, 2000; 1033–52

4 Bendixen D, Skovgaard LT, Ording H. Analysis of anaesthesia in patients suspected to be susceptible to malignant hyperthermia before diagnostic *in vitro* contracture test. *Acta Anaesthesiol Scand* 1997; **41**: 480–4

5 Puschel K, Schubert-Thiele I, Hirth L, Benkmann HG, Brinkmann B. Malignant hyperthermia during the 13th general anaesthesia. *Anaesthesist* 1978; **27**: 488–91

6 Larach MG, Localio AR, Allen GC, *et al.* A clinical grading scale to predict malignant hyperthermia susceptibility. *Anesthesiology* 1994; **80**: 771–9

7 MacLennan DH, Phillips MS. Malignant hyperthermia. *Science* 1992; **256**· 789–94

8 Ording H. Diagnosis of susceptibility to malignant hyperthermia in man. *Br J Anaesth* 1988; **60**· 287–302

9 European Malignant Hyperpyrexia Group. A protocol for the investigation of malignant hyperpyrexia (MH) susceptibility. *Br J Anaesth* 1984; **56**: 1267–9

10 Iaizzo PA, Klein W, Lehmann-Horn F. Fura-2 detected myoplasmic calcium and its correlation with contracture force in skeletal muscle from normal and malignant hyperthermia susceptible pigs. *Pflugers Arch* 1988; **411**. 648–53

11 Mickelson JR, Gallant EM, Litterer LA, *et al* Abnormal sarcoplasmic reticulum ryanodine receptor in malignant hyperthermia *J Biol Chem* 1988; **263**. 9310–5

12 McCarthy TV, Healy JM, Heffron JJ, *et al.* Localization of the malignant hyperthermia susceptibility locus to human chromosome 19q12–13.2. *Nature* 1990; **343**. 562–4

13 Fujii J, Otsu K, Zorzato F, *et al* Identification of a mutation in porcine ryanodine receptor associated with malignant hyperthermia. *Science* 1991; **253**: 448–51

14 Manning BM, Quane KA, Ording H, *et al.* Identification of novel mutations in the ryanodine-receptor gene (ryr1) in malignant hyperthermia: Genotype-phenotype correlation *Am J Hum Genet* 1998; **62**: 599–609

15 Robinson RL, Monnier N, Wolz W, *et al* A genome wide search for susceptibility loci in three european malignant hyperthermia pedigrees. *Hum Mol Genet* 1997; **6**: 953–61

16 Jurkat-Rott K, McCarthy T, Lehmann-Horn F. Genetics and pathogenesis of malignant hyperthermia. *Muscle Nerve* 2000; **23**. 4–17

17 Censier K, Urwyler A, Zorzato F, Treves S. Intracellular calcium homeostasis in human primary muscle cells from malignant hyperthermia-susceptible and normal individuals. Effect of overexpression of recombinant wild-type and arg163cys mutated ryanodine receptors. *J Clin Invest* 1998; **101**. 1233–42

18 Grynkiewicz G, Poenie M, Tsien RY. A new generation of Ca^{2+} indicators with greatly improved fluorescence properties. *J Biol Chem* 1985; **260**· 3440–50

19 Girard T, Urwyler A, Censier K, *et al* Genotype-phenotype comparison of the swiss malignant hyperhermia population. *Hum Mutat* 2001; **18**· 357–8

20 Ording H, Brancadoro V, Cozzolino S, *et al.* *In vitro* contracture test for diagnosis of malignant hyperthermia following the protocol of the European MH Group. Results of testing patients surviving fulminant mh and unrelated low-risk subjects. The european malignant hyperthermia group. *Acta Anaesthesiol Scand* 1997; **41**: 955–66

21 Tong J, Oyamada H, Demaurex N, *et al.* Caffeine and halothane sensitivity of intracellular Ca^{2+} release is altered by 15 calcium release channel (ryanodine receptor) mutations associated with malignant hyperthermia and/or central core disease *J Biol Chem* 1997, **272**: 26332–9

22 Urwyler A, Deufel T, McCarthy T, West S. Guidelines for molecular genetic detection of susceptibility to malignant hyperthermia. *Br J Anaesth* 2001, **86**. 283–7

British Journal of Anaesthesia **89** (4). 580–5 (2002)

Pharmacodynamics of mivacurium chloride in 13- to 18-yr-old adolescents with thermal injury

J. A. J. Martyn[1]*, Y. Chang[1], N. G. Goudsouzian[1] and S. S. Patel[2]

[1]Department of Anesthesiology and Critical Care, Harvard Medical School, Massachusetts General Hospital and Shriners Hospital for Children, Boston, MA 02114, USA. [2]Anaesthesia Clinical Research, GlaxoWellcome, Research Triangle Park, NC 27709, USA

**Corresponding author*

Background. Burned patients demonstrate resistance to the effects of non-depolarizing blocking drugs as a result of acetylcholine receptor changes. They also have decreased activity of plasma cholinesterase (PCHE), which metabolizes mivacurium. We hypothesized that decreased PCHE activity would decrease metabolism of mivacurium, and counteract the receptor-related resistance following burns.

Methods. Thirteen burned patients and six controls, aged 13–18 yr were followed in 27 studies. The burned patients were sub-classified as having 10–30% or >30% body surface area burn and were studied whenever possible at ≤6 days, and at 1–12 weeks after the burn. Mivacurium pharmacodynamics were examined following a bolus (0.15 mg kg^{-1}) dose, and during and after a continuous infusion.

Results. Following a bolus, the onset time and the maximal effect were similar to controls. Recovery was prolonged in the 10–30% burn group at 1–12 weeks ($P<0.008$), with a similar trend in the >30% burn group at ≤6 days ($P<0.082$) compared with controls. The infusion requirements for mivacurium were not increased in the burned groups. The PCHE activity was decreased in all burn groups and was inversely related to recovery following the bolus ($r=0.73$, $P<0.001$) and the infusion ($r=0.69$, $P<0.001$).

Conclusion. In contrast to previous studies with non-depolarizers in burned patients, normal mivacurium doses can produce paralysis, at least as rapidly as in controls, but with a possibility of a prolonged recovery from block. The standard dose of mivacurium in the presence of decreased PCHE activity is in effect, a relative overdose that explains the above findings. Mivacurium is an effective drug for use in burns, irrespective of time after, or magnitude of burn injury.

Br J Anaesth 2002; **89**: 580–5

Keywords: complications, burn injury; enzymes, plasma cholinesterase; neuromuscular block, mivacurium

Accepted for publication: June 10, 2002

Typically, burned patients exhibit resistance to the effects of non-depolarizing neuromuscular blocking drugs.[1 2] This resistance is usually seen in patients with ≥25–30% total body surface area (TBSA) burn, and it takes approximately 1 week to develop. The resistance to non-depolarizing neuromuscular blocking drugs is mostly related to qualitative changes (mature to immature receptor isoform conversion), and quantitative increases in the numbers of receptors.[1 2] Mivacurium is a short-acting non-depolarizing neuromuscular blocking drug, which undergoes hydrolysis by the enzyme plasma cholinesterase (PCHE). Burned patients have decreased PCHE activity.[3] This decreased enzyme activity is dependent on the magnitude of, and time after, burn injury.[3 4] We have recently found a lack of resistance to mivacurium chloride in 2- to 12-yr-old patients with burn injury, when recommended doses of the drug were administered.[5] A comparison of PCHE activity *vs* recovery from neuromuscular block indicated an inverse relationship between the two variables. An important variable affecting the response to drugs is age, and in

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

addition to others, we have shown neuromuscular responses to be different between children and adolescents.[6] Therefore, as an extension of the study in children, we present data relating to the neuromuscular effects of mivacurium in 13- to 18-yr-old adolescents. In the present study in adolescents with burn injury, the pharmacodynamics of mivacurium were examined in relation to the size of burn, time after burn, PCHE activity, and dibucaine number.

Methods

Patients and study procedure

This study was approved by the Sub-committee on Human Studies, Committee on Research of the Massachusetts General Hospital, Boston, Massachusetts. Written informed consent was obtained from the patient and/or from the parent or guardian of all patients and controls included in the study. Twenty-one adolescent burned patients aged 13–18 yr, ASA physical status I–III, undergoing surgery consequent to thermal burn injury, were enrolled. The control group consisted of an additional six patients who had been burned more than 3 yr before the study. This control group was used, based on previous and current clinical observations that neuromuscular responses to relaxants are normal by 3 yr after burn injury, provided other confounding factors are absent.[2] The acutely burned patients were sub-classified according to burn size as having 10–30% or >30% TBSA burn. Each of these (10–30% or >30% TBSA) burn groups was divided into sub-groups according to the time of the study: ≤6 days, or 1–12 weeks after burn injury. For each subject who was studied at ≤6 days after burn injury, every attempt was made to re-enroll that subject for a subsequent study at 1–12 weeks after the injury. The four burn groups in this study, based on burn size and time after burn injury, are summarized in Table 1. Two subjects, each with 10–30% and >30% TBSA burn, were not studied initially at ≤6 days after burn because of delayed transfer to the burn unit, but were studied at 1–12 weeks after injury. One subject with 10–30% burns did not participate in the second study at 1–12 weeks.

Patients who were obese or had evidence of clinically significant asthma, renal, hepatic, psychiatric, neurological, neuromuscular, or cardiovascular disease were excluded from the study. Patients were also excluded if medications known to influence neuromuscular transmission were administered, or if clinically significant abnormalities in haematology (haemoglobin and platelet and white blood cell counts), and clinical chemistry tests (creatinine, alkaline phosphatase, or liver transaminases) were present. Venous blood was sampled at the time of the study to determine PCHE activity and dibucaine number.

Anaesthesia

Preoperative medication consisted of a benzodiazepine and/or narcotic, administered orally or i.v. depending on the presence or absence of an i.v. line. Monitoring consisted of electrocardiography, non-invasive arterial pressure (except in those patients who had an indwelling arterial cannula), pulse oximetry, end-tidal carbon dioxide, and temperature continuously. Anaesthesia was induced with propofol, or halothane (0.25–3% end-tidal concentration) in oxygen by a mask; supplemental bolus doses of fentanyl were administered as necessary during induction. Anaesthesia was maintained with halothane (0.5–1.0% end-tidal), nitrous oxide, and oxygen. During maintenance of anaesthesia, propofol (1 mg kg^{-1} i.v. bolus doses) along with narcotic agents (fentanyl 1–2 μg kg^{-1} or morphine 0.1–0.2 mg kg^{-1}) were administered as anaesthetic supplements. Ventilation was controlled to maintain normocapnia.

Pharmacodynamics

After induction of anaesthesia, the ulnar nerve was stimulated with a Grass S48 stimulator through 25-gauge needles inserted into a forearm, immobilized on a padded board. The thumb was linked to a Grass FT03 force transducer, and the evoked twitch tension of the adductor pollicis was recorded as twitch height on a Grass strip-chart recorder. Single square-wave stimuli of 0.2 ms duration were administered at 0.15 Hz. An initial tetanus of 30 s duration was administered to recruit all muscle fibres. Control twitch height was obtained from a stable baseline recording of at least 5 min

Table 1 Design of data collection from burn patient

	≤6 days	**1–12 weeks**
10–30% burn	*n*=4 (1 complete, 2 bolus studies only) – (*n*=1 gentamicin during bolus therefore not reported) – (*n*=2 gentamicin after bolus during infusion, infusion data not reported) – (*n*=1 complete study)	*n*=5 (all studies completed) – (*n*=3 studied earlier) – (*n*=2 new patients not studied earlier)
>30% burn	*n*=5 (4 complete studies) – (*n*=1 gentamicin during bolus, therefore not reported)	– *n*=7 (6 complete, 1 bolus only studies) – (*n*=5 studied earlier) – (*n*=2 new patients not studied earlier) – (*n*=1 gentamicin after bolus, therefore infusion data not reported)

before the administration of mivacurium. Initially, mivacurium was administered as a bolus (0.15 mg kg^{-1}) and later as an infusion. Towards the end of the surgical procedure, the continuous infusion of mivacurium was stopped. Following termination of the infusion, the stimulation mode was changed to supramaximal train-of-four stimuli (0.2 ms square waves), administered at 2 Hz. End-control twitch height was determined after at least 3 min recording a stable height of the first twitch of the train-of-four, and the train-of-four ratio (T_4:T_1) of ≥75%.

Intubation proceeded 2–5 min after the initial dose of mivacurium, when maximal twitch suppression was reached. The recovery of the twitch to 25% of baseline (control) height was monitored. The second part of the study consisted of a continuous infusion of mivacurium. Following recovery of the twitch after the bolus dose to 25%, additional mivacurium bolus doses were administered, followed by a continuous infusion to maintain neuromuscular suppression at 95 (SD 4)% (i.e. 5 (4)% initial twitch height). The continuous infusion rate was started at 20 µg kg^{-1} min^{-1} and adjusted every 3 min, if necessary, in increments or decrements of 1–2 µg kg^{-1} min^{-1} to maintain neuromuscular block within the range of 95 (4)%.

The following variables were determined: following bolus doses, the maximum twitch suppression, onset time (from completion of mivacurium injection to maximum twitch suppression), and clinically effective duration time (from completion of injection of the bolus dose to 25% twitch recovery). Times were also noted after stopping the continuous infusion to 25, 75, and 95% recovery of the first twitch of the train-of-four relative to end-control, and to T_4:T_1 ≥75%. Average infusion rates for each patient who received a continuous infusion for a minimum of 30 min were also recorded.

Data analysis

Analysis of variance techniques were used to compare outcomes between groups. As a result of the small sample size of the study, statistical tests were restricted to comparisons between each burn group and controls. That is, no intra-burn group comparisons were made. Adjusted P values were reported from Dunnett multiple comparisons procedure. Pearson correlation coefficient (r) was used to summarize the relationship between PCHE activity and recovery time. A $P<0.05$ was considered statistically significant.

Results

Two patients received gentamicin during the bolus-dose part of the study and their data, including physical characteristics, are not reported (Table 1). Three patients received i.v. gentamicin after the initial bolus dose of mivacurium had been given, and after 25% recovery of the single twitch response. This neuromuscular data was used for analysis of the bolus studies, but not of the infusion studies. Only patients whose data were usable are reported in Tables 2–5. Thus, the physical characteristics and neuromuscular data of 13 burned (total of 19 studies) and six controls (total six studies) are reported.

The study population was comparable between groups (Table 2). At the recommended dose of mivacurium 0.15 mg kg^{-1}, profound neuromuscular block was achieved in all patients (Table 3). Both groups of burned patients studied after 1–12 weeks achieved more rapid relaxation than the other sub-groups, although this effect was not statistically significant (P=0.092 for 10–30% burn and P=0.066 for >30% burn compared with controls). The trend for a faster onset of effect at ≤6 days for both burn groups also did not

Table 2 Physical characteristics of patients Mean (SD), TBSA=total body surface area

Burn size (%TBSA)	Time of study after burn injury	Age (yr)	Weight (kg)	Sex (male/female)	ASA physical status (I/II/III)	Ethnic origin (White/Black/Other)
10–30	≤6 days	14.3 (13.2–15.0)	51.9 (7.3)	2/1	0/2/1	3/0/0
10–30	1–12 weeks	15.2 (13.2–17.3)	60.2 (11.9)	3/2	1/3/1	4/0/1
>30	≤6 days	15.6 (14.7–17.7)	69.5 (14.6)	3/1	0/1/3	4/0/0
>30	1–12 weeks	15.5 (13.8–17.8)	58.2 (15.7)	5/2	0/5/2	6/0/1
Control	>3 yr after burn	16.4 (14.4–18.4)	63.5 (7.9)	2/4	5/1/0	3/0/3

Table 3 Pharmacodynamics of mivacurium after bolus dose Values are mean [SEM], number of patients is in parentheses *$P<0.05$ compared with controls, **$0.05<P<0.10$ compared with controls

Burn size (%TBSA)	Time of study after burn injury	Maximum suppression (%)	Time (min) to:	
			Maximum suppression	25% recovery of twitch
10–30	≤6 days	99 [1] (3)	3.3 [0.4] (3)	20 [4] (3)
10–30	1–12 weeks	100 [0.0] (5)	3.2 [0.3]** (5)	22 [2]* (4)
>30	≤6 days	99 [1] (4)	3.4 [0.4] (4)	22 [4]** (4)
>30	1–12 weeks	95 [4] (7)	3.1 [0.4]** (7)	18 [2] (5)
Control	>3 yr after burn	96 [3] (6)	4.6 [0.6] (6)	13 [1] (5)

Table 4 Mivacurium pharmacodynamics during and after continuous infusion. Values are mean [SEM], number of patients in parenthesis *$P<0.05$ compared with controls

Burn size (%TBSA)	Time of study after burn injury	Height of single twitch at the end of infusion (%)	Duration of infusion (min)	Mean infusion rate ($\mu g\ kg^{-1}\ min^{-1}$)	Recovery profiles time (min): To T_4:T_1 ratio ≥75%	To 95% of T_1 in train-of-four	From 25 to 75% of T_1 in train-of-four
10–30	<6 days	1.0 [–] (1)	34.0 [–] (1)	5.5 [–] (1)	20 [–] (1)	18 [–] (1)	7 [–] (1)
10–30	1–12 weeks	3 [1] (4)	63 [7] (4)	4 [1]* (4)	25 [3] (4)	23 [2] (4)	9 [1] (3)
>30	<6 days	4 [1] (4)	77 [12] (4)	5 [1]* (5)	33 [5]* (4)	29 [5]* (4)	12 [2]* (4)
>30	1–12 weeks	4 [2] (6)	61 [11] (7)	11 [3] (5)	24 [5] (6)	23 [3] (6)	8 [2] (6)
Control	>3 yr after burn	2 [1] (6)	76 [13] (6)	9 [1] (6)	15 [1] (6)	15 [1] (6)	5 [1] (6)

Table 5 Mean PCHE activity and dibucaine number *Mean [SEM]; number of studies in parenthesis, $^+$range, **$P<0.001$ compared with controls

Burn size (%TBSA)	Time of study after burn injury	Dibucaine number (%)$^+$	PCHE activity* (IU ml^{-1})
10–30	≤6 days	60–81 (3)	1.6 [0.5]** (3)
10–30	1–12 weeks	65–84 (3)	1.7 [0.1]** (4)
>30	≤6 days	73–81 (3)	1.6 [0.4]** (4)
>30	1–12 weeks	71–90 (7)	2.2 [0.5]** (7)
Control	>3 yr after burn	79–82 (6)	4.9 [0.2] (6)

attain statistical significance (Table 3). For patients with small (10–30%) burns, studied 1–12 weeks after injury, recovery of the single twitch height to 25% following the bolus dose of mivacurium was longer than that of patients in the control group (Table 3, $P=0.008$). In patients with >30% burns studied ≤6 days after injury, this difference did not reach statistical significance ($P=0.082$).

With the exception of the small (10–30%) burn group studied ≤6 days after injury, the average duration of continuous infusion was comparable between groups (Table 4). Mean infusion rate for patients with small burns (10–30%) studied at 1–12 weeks, and those with >30% burns studied at ≤6 days after injury, were significantly lower than controls. The recovery profiles following termination of the infusion for all groups of burned patients, particularly in patients with >30% TBSA burns studied ≤6 days after injury, showed slower rate of recovery compared with controls ($P=0.05$, 0.028, and 0.004 for time to T_4:T_1 ratio ≥75%, time to 95% recovery of T_1 in train-of-four, and time from 25 to 75% of T_1 in train-of-four, respectively).

The dibucaine numbers of patients with burn injury were comparable with those for the control group, irrespective of the time after burn or the size of burn injury (Table 5). Mean PCHE activity following burn injury was significantly suppressed compared with that of the control group (all $P=0.001$). There was no observable difference in the PCHE activity when related to time after, or magnitude of, burn injury. Regression analysis of pooled data from controls and burns indicated that recovery from mivacurium block was inversely related to PCHE activity; the lower the PCHE activity the longer the recovery. This relationship was observed both after the bolus ($r=-0.73$, $P<0.001$), and the infusion ($r=-0.69$, $P<0.001$) (Fig. 1). A curvilinear plot did not significantly improve the regression line.

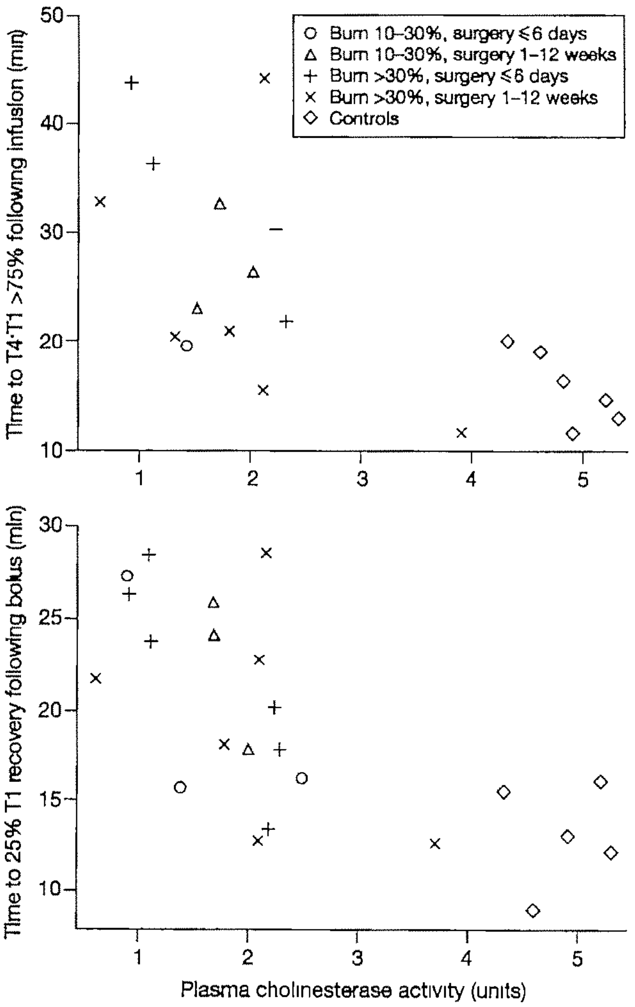


Fig 1 Correlation of PCHE activity to recovery from block, following infusion (upper figure) and bolus (lower figure). There was a significant inverse relationship between PCHE and recovery, following the infusion ($R^2=0.49$, $r=-0.7$, $P<0.001$) and the bolus ($R^2=0.53$, $r=-0.73$, $P<0.001$).

Discussion

The purpose of these studies was to examine the effects of burn size and time after burn on the neuromuscular effects of mivacurium. If all patients had received gentamicin at the same time, it would have been appropriate to include all of them and study the neuromuscular effects of mivacurium when combined with gentamicin. Because of the confounding pharmacodynamic effects of gentamicin when co-administered with neuromuscular blocking drugs, it was justifiable that patients receiving gentamicin be excluded. This resulted in a decrease in number per group, with the potential for type II error in the data. Despite the paucity of numbers, a major weakness of this study, statistical significance was still observed, and therefore certain definitive conclusions can be made.

The salient findings in this study of mivacurium pharmacodynamics in burned and control adolescent patients were: (1) a trend to a faster onset time in burn patients compared with controls (Table 3), with maximal effect similar in all groups; (2) the profiles of neuromuscular recovery being similar to, or prolonged in burned patients relative to controls after bolus doses and continuous infusions (Table 4); (3) with the exception of >30% burn at 1–12 weeks, the mean infusion rates were decreased in the burn groups compared with controls (Table 4); and (4) PCHE levels, but not dibucaine levels, were decreased in burned patients (Table 4) with an inverse relationship between PCHE activity and the recovery profile (Fig. 1).

Burned patients have resistance to both benzylisoquinoline and steroidal neuromuscular blocking drugs,[7–12] demonstrated as inadequate paralysis from an ED_{95} dose, a requirement for higher doses for a given effect, prolonged onset of effect, faster recovery, more frequent dosing intervals, and/or higher infusion rates The present results with mivacurium fulfil none of these criteria for resistance. The onset was similar to or faster than controls, maximal effects were the same, recovery rates were the same or prolonged, and infusion rates were similar or lower in burned patients compared to controls. This study shows evidence of prolonged recovery, which suggests that burned adolescents may demonstrate increased sensitivity to mivacurium. This study is therefore, consistent with previous studies of mivacurium in children[5] and adults,[13] showing that burned patients do not exhibit resistance to mivacurium. The adult study, however, did not discriminate between the effects of burn size and time after burn on pharmacodynamics or PCHE activity.

Causes for the resistance to non-depolarizers following burns include: increased protein binding;[14] enhanced clearance kinetics;[15 16] and most importantly, upregulation of acetylcholine receptors.[17 18] Although acetylcholine receptor changes were not quantified in this study, one can assume, based on previous animal[1 17 18] and human studies,[19] that qualitative and quantitative changes were present at the muscle membrane, especially in patients with the bigger burns at 1–12 weeks after injury. One may be surprised, therefore, that our burned patients did not demonstrate resistance to the competitive neuromuscular blockers, mivacurium.

The rationale for sub-classification of our burn groups was to quantify the effect of time after burn, and magnitude of burn on mivacurium pharmacodynamics. The PCHE activity was decreased in all burn groups. In 10–30% TBSA burned patients, resistance will not be seen at any time, as clinically significant receptor changes usually do not occur with minor burns. Even in patients with >30% burn at ≤6 days, receptor changes are not expected. Thus, the lower mivacurium infusion rates relative to controls, observed in the 10–30% burn group at 1–12 weeks, and >30% group at ≤6 days, may be related to a lower PCHE activity in the absence of upregulation of acetylcholine receptors. In contrast, in patients with >30% burns studied at 1–12 weeks after the insult, resistance to non-depolarizing neuromuscular blockers usually occurs because of receptor changes. In the present study, receptor changes were probably present in these patients, as the infusion requirement of mivacurium was similar to that of controls, despite the lower PCHE activity. This suggests that resistance had developed to mivacurium at the receptor level, but the kinetic effect of lowered metabolism counteracted this resistance, resulting in an infusion rate similar to controls. In other words, the receptor-related (dynamic) resistance was counterbalanced by the kinetic component, decreased metabolism of mivacurium because of depressed PCHE activity.

The dibucaine numbers were not different between groups, and therefore one can rule out hereditary factors or qualitative changes in PCHE activity, causing prolonged recovery from mivacurium in the burned patients. The PCHE activities, however, were lower in all burned patients (Table 5 and Fig. 1). Thus, the usual bolus dose of mivacurium 0.15 mg kg^{-1} in the presence of decreased PCHE activity is a relative overdose. This explanation is consistent with findings in other diseases associated with acquired decreases in PCHE activity. The onset of effect with mivacurium can be similar or faster but recovery is prolonged.[20 21] Our study also confirms an inverse relationship between PCHE activity and recovery from paralysis following a bolus dose or infusion. These findings are consistent with other observations of the importance of PCHE in the recovery from mivacurium.[22]

A good substitute for succinylcholine for use in burned patients is currently not available. Rapid onset of paralysis for intubation of burned patients with a full stomach, or for the treatment of laryngospasm requires higher than normal doses of non-depolarizing relaxants.[2 24] The prolonged onset of effect is a serious disadvantage when treating laryngospasm in burned patients, who can desaturate rapidly because of the hypermetabolic state and poor lung function.[25] This study documents that normal (ED_{95}) doses of mivacurium, can produce effective paralysis, at least as rapidly as in normal patients.

Acknowledgements

Supported in part by grants (to J A J.M.) from GlaxoWellcome, Shriners Hospitals for Children and from National Institutes of Health, GM31569-20, GM55082-6, and GM61411-4

References

1 Ibebunjo C, Martyn JAJ. Thermal injury induces greater resistance to d-tubocurarine in local than in distant muscles in the rat. *Anesth Analg* 2000; **91**: 1243–9

2 Martyn JAJ, White DA, Gronert GH, Jaffe RS, Ward J. Up- and down-regulation of skeletal muscle acetylcholine receptors. Effects on neuromuscular blockers. *Anesthesiology* 1992; **76**: 822–43

3 Viby-Mogensen J, Hanel HK, Hansen E, Sorensen B, Graae J. Serum cholinesterase activity in burned patients I: biochemical findings *Acta Anaesthesiol Scand* 1975; **19**: 159–68

4 Kamolz LP, Andel H, Greher M, Ploner M, Meissl G, Frey M Serum cholinesterase activity reflects morbidity in burned patients. *Burns* 2002; **28**: 47–50

5 Martyn JAJ, Goudsouzian NG, Chang YC, Szyfelbein SK, Schwartz AE, Patel SS. Neuromuscular effects of mivacurium in 2- to 12-yr-old children with burn injury. *Anesthesiology* 2000; **92**: 31–7

6 Goudsouzian NG, Martyn JAJ. Potentiation of mivacurium by rocuronium is age- and time dependent: a study in children, adolescents and young and elderly adults. *J Clin Pharmacol* 1997; **37**: 649–55

7 Mills AK, Martyn JAJ. Evaluation of atracurium neuromuscular blockade in paediatric patients with burn injury. *Br J Anaesth* 1988; **60**. 450–5

8 Dwersteg JF, Pavlin EG, Heimbach DM. Patients with burns are resistant to atracurium. *Anesthesiology* 1986, **65**: 517–20

9 Mills AK, Martyn JAJ. Neuromuscular blockade with vecuronium in paediatric patients with burn injury. *Br J Clin Pharmac* 1989; **28**: 155–9

10 Martyn JAJ, Liu LMP, Szyfelbein SK, Ambalavanar ES, Goudsouzian NG. The neuromuscular effects of pancuronium in burned children. *Anesthesiology* 1983, **59**: 561–4

11 Martyn JAJ, Goudsouzian NG, Matteo RS, Liu LMP, Szyfelbein SK, Kaplan RF. Metocurine requirements and plasma concentrations in burned paediatric patients. *Br J Anaesth* 1983; **55**: 263–8

12 Marathe PH, Dwersteg JF, Pavlin EG, Haschke RH, Heimbach DM, Slattery JT. Effect of thermal injury on the pharmacokinetics and pharmacodynmics of atracurium in humans *Anesthesiology* 1989; **70**: 752–5

13 Werba AE, Neiger FX, Bayer GS, Schultz AM, Maitz PKM, Wolrab CH. Pharmacodynamics of mivacurium in severely burned patients. *Burns* 1996; **22**: 62–4

14 Martyn JAJ, Abernathy DR, Greenblatt DJ. Plasma protein binding of drugs after burn injury. *Clin Pharmacol Ther* 1984; **35**: 535–9

15 Martyn JAJ, Bishop AL, Oliveri MF. Pharmacokinetics and pharmacodynamics of ranitidine after burn injury. *Clin Pharmacol Ther* 1992; **51**: 408–14

16 Martyn JAJ. Clinical pharmacology and drug therapy in the burned patient *Anesthesiology* 1986, **65**: 67–75

17 Kim C, Martyn JAJ, Fuke N. Burn injury to trunk of rat causes denervation-like responses in the gastrocnemius muscle *J Appl Physiol* 1988; **65**: 1745–51

18 Ibebunjo C, Martyn JAJ. Disparate dysfunction of skeletal muscles located near to and distant from burn site in the rat. *Muscle Nerve* 2001; **24**: 1283–94

19 Perov S, Prasad JK, Nagelhout J, Walczyk W, Martyn JAJ Upregulation of acetylcholine in a severely burned patient *Anesthesiology* 1994; **81**: A1089

20 Ostergaard D, Jensen FS, Jensen E, Skovgaard LT, Viby-Mogensen J. Influence of plasma cholinesterase activity on recovery from mivacurium-induced neuromuscular blockade in phenotypically normal patients *Acta Anaesth Scand* 1992; **36**. 702–6

21 Beaufort TM, Nigrovic V, Proost JH, Howertjes MC, Wierda JMKH. Inhibition of enzyme degradation of suxamethonium and mivacurium increases onset time of submaximal neuromuscular block. *Anesthesiology* 1998, **89**: 707–14

22 Markakis DA, Hart PS, Lau M, Brown R, Fisher DM. Does age or pseudocholinesterase activity predict mivacurium infusion rate in children? *Anesth Analg* 1996; **82**: 39–43

23 Martyn JAJ. Succinylcholine hyperkalemia after burns. *Anesthesiology* 1999; **91**: 321–2

24 Hagen J, Martyn JAJ, Szyfelbein SKS, Goudsouzian NG. Cardiovascular and neuromuscular responses to high-dose pancuronium-metocurine in pediatric burned and reconstructive patients. *Anesth Analg* 1986; **65**. 1340–5

25 Abdi S, Cortilla J, Martyn JAJ. Burn-injury related anesthetic emergencies. *Semin Anesth* 1998; **17**: 139–46

British Journal of Anaesthesia 89 (4): 586–93 (2002)

Training course in local anaesthesia of the airway and fibreoptic intubation using course delegates as subjects

V. Patil*, G. L. Barker, R. J. Harwood and N. M. Woodall

Department of Anaesthetics, Norfolk and Norwich University Hospital NHS Trust, Colney Lane, Norwich NR4 7UZ, UK

**Corresponding author: Department of Anaesthetics, James Paget Hospital, Lowestoft Road, Great Yarmouth, Norfolk NR31 6LA, UK*

Background. We describe a practical method of training anaesthetists in the technique of awake fibreoptic intubation. This is performed on a training course using the delegates as subjects.

Methods. The first 15 subjects underwent cardiovascular monitoring during airway fibreoptic endoscopy performed by other course members. They were subsequently interrogated by use of a questionnaire.

Results. Evidence from questionnaires suggests this method of instruction is acceptable in this self-selected group of individuals. Gagging was the commonest unpleasant side-effect of airway endoscopy, although only one delegate rated this as uncomfortable. Fifty-four per cent of subjects found the procedure slightly painful; 46% reported no pain at all. Overall, the procedure was rated as acceptable by 85% of subjects and enjoyable by 15% of subjects. No delegate found endoscopy or intubation distressing. Cardiovascular monitoring revealed pulse rate and arterial pressure changes of less than 25% of baseline values. Paraesthesia developed in one individual and nasal bleeding in two cases, neither of which was clinically significant and did not interfere with endoscopy.

Conclusions. The use of course delegates as subjects for training was acceptable to anaesthetists and is associated with a low level of discomfort and morbidity.

Br J Anaesth 2002; **89**: 586–93

Keywords: intubation tracheal; education

Accepted for publication: May 29, 2002

Provision of training on local anaesthesia of the airway and fibreoptic endoscopy is difficult for many reasons including a lack of suitable patients, ethical considerations and time pressure in the clinical environment.[1] For these reasons, we designed a course to enable delegates to develop, refine and practice their skills in airway anaesthesia and endoscopy of live human subjects. Mannequins and models offer an alternative but are anatomically unrealistic, over-simplified, immobile, uncontaminated with secretions, and do not offer an adequate challenge. Mannequins help to develop motor skills, but do little to build the confidence necessary for use in a clinical situation. Though our method of training does not provide instruction in the management of specific airway problems, it does enable familiarization with normal human endoscopic anatomy. In a course of six participants and two observers, each participant would be expected to perform at least four nasendoscopies to the level of the larynx and a further endoscopy to the carina, followed by the passage of a tracheal tube over the endoscope. With the aid of a video-display system, each delegate should also witness a further 20 nasendoscopies and directly observe the passage of five tracheal tubes.

In this paper, we report complications and assess the satisfaction of delegates attending this course.

Methods

The course is open to anaesthetists of all grades. There are two levels of entry, as an observer or as a participant. All participants receive an explicit warning of the risks of the procedure. Observers do not participate in all practical sessions and do not undergo endoscopy. Information is

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

provided on an application form (Appendix A), with a detailed subjective description of endoscopy and intubation (Appendix B), in addition to an explicit consent form (Appendix C). Participants complete a consent form on application. Consent is reaffirmed immediately prior to undergoing endoscopy. Our trust (Norfolk and Norwich Hospital University Hospital NHS Trust) solicitors were consulted in order to ensure that the trust's liabilities would be covered in the event of a serious complication.

Delegates with a history of the following conditions were excluded as participants: nose problems, any infectious disease, hypertension, heart disease, liver disease, epilepsy, diabetes, asthma or pregnancy.

In common with many other courses, instruction is provided in care of the endoscope, endoscopy technique, airway anatomy, indications for awake intubation, local anaesthesia of the airway, and tracheal intubation. Lectures and video demonstrations are supported by practical sessions using mannequins and the artificial throat endoscopy model.[2] During practical endoscopy sessions on models and mannequins, delegates are divided into small groups, each under the supervision of an instructor in order to ensure all delegates understand and can demonstrate the practical principles of endoscopy. All participants were informed that if they found the endoscopy or intubation uncomfortable or wanted to stop, they should raise their arm. Further local anaesthetic could then be administered or the procedure would be abandoned.

Human endoscopy sessions take place in an operating theatre with full resuscitation facilities available. Video cameras are used with all endoscopes and provide multiple viewing screens. All endoscopists wear operating theatre clothes and gloves; gloves are discarded after each procedure. Endoscopes undergo routine disinfection between subjects in line with our trust/hospital policy. This policy involves glutaraldehyde disinfection with a contact time of 20 min, as currently recommended by the British Thoracic Society.[3] All endoscopes are leak tested at the beginning and end of each session.

Prior to performing endoscopy on course participants, all delegates perform endoscopy on an instructor, the delegate passes a nasotracheal tube. The following day, participating delegates act as endoscopy subjects following a 4-h fast.

Routine baseline monitoring of non-invasive arterial pressure, continuous oximetry and ECG is established, then recorded at 5-min intervals throughout the procedure. Intravenous access is gained with a 20-gauge cannula and i.v. glycopyrrolate 3 μg kg^{-1} is administered as an antisialagogue, to improve the view and to enhance local anaesthetic effectiveness.[4] This is followed by two puffs of 0.1% xylometazoline to each nostril prior to topical anaesthesia of the airway. Nebulized 4% lidocaine 160 mg is delivered over a 10-min period using a standard Intersurgical nebulizer with oxygen 10 litre min^{-1} as a driving gas. Superficial nasendoscopy is performed to select the largest nostril for local anaesthesia, endoscopy and intubation. The selected nostril is anaesthetised with 2.5 ml of 5% lidocaine solution containing 0.5% phenylephrine. After insertion of the endoscope, further doses of 4% lidocaine are administered to the lower airway via the working channel of the endoscope using an epidural catheter with an end hole as a conduit, in the manner described by O'Hare.[5] Subjects are asked to take slow regular deep breaths to facilitate distribution of local anaesthetic spray. Laryngeal anaesthesia is judged to be adequate when the larynx ceases to react to the application of local anaesthetic. This is then followed by further local anaesthetic administration to the lower airway. The maximum dose of topical lidocaine is limited to 9 mg kg^{-1}.[6] Nasotracheal intubation using a Portex Ivory blue line tube is then performed by a participating delegate under the direct supervision of the instructors.

If the nasal cavity was found to be too small to permit the passage of a Keymed LF-GP fibreoptic laryngoscope or a 6.0-mm uncuffed nasotracheal tube, intubation was abandoned. No sedation or local or i.v. anaesthetic injections were administered. Supplemental oxygen was administered to all delegates via nasal cannulae during airway endoscopy. Oxygen saturation, heart rate and arterial pressure recordings were continued until completion of intubation and removal of the tracheal tube.

Data were collected from the application forms about the sex, seniority and previous endoscopy experience of all delegates.

On completion of the course, all participants completed a feedback form (Appendix D) They were asked to grade the acceptability of endoscopy and intubation with regard to pain, anxiety, coughing, and gagging. In addition, they were asked to report any other adverse experiences. All delegates were asked to give an overall evaluation of the course on a graded scale of very poor to excellent. Heart rate and arterial pressure measurements of two instructors who underwent demonstration endoscopy are included in this report; feedback forms were not collected from them.

Following the practical session, delegates were given direct feedback from their supervising instructor. Instructors emphasize that the course is only a part of the training they will need in airway management. In addition, they give advice on how to develop and maintain endoscopy skills.

Results

Background information

Data were collected from 15 subjects on three separate courses over a period of 6 months. There were 11 males and four females, with an age range of 25–50 yr.

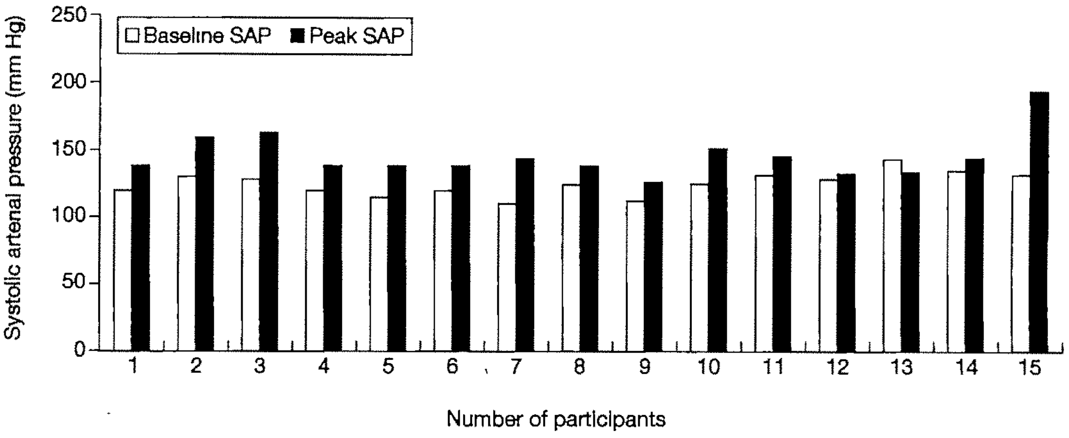


Fig 1 Baseline and peak systolic arterial pressure of the participants.

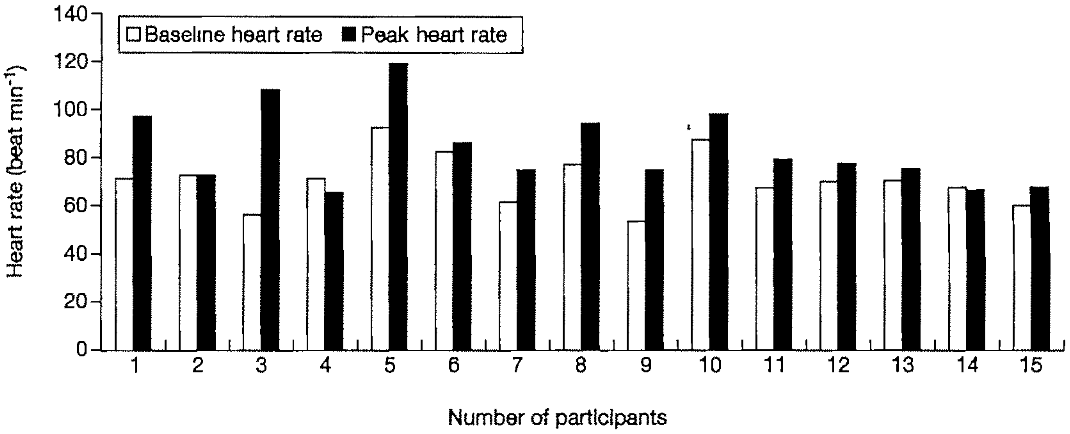


Fig 2 Baseline and peak heart rate of the participants.

Previous experience

The experience level of our course delegates was diverse. Six delegates had performed fewer than five endoscopies each. Two had performed one each and two delegates had no previous experience at all. The average previous experience was 19 endoscopies; however, this was skewed by two individuals who had both performed over 50, and by five others who had performed 25 or more. One delegate had performed 12 solo endoscopies, having never performed one under supervision. Six delegates had never performed an awake intubation whilst two delegates had experience of five awake intubations.

Duration of procedure

The duration of each procedure varied from 35 to 70 min with an average duration of 55 min. The number of heart rate and arterial pressure estimations varied from 8 to 15 per subject with an average of 12.

Haemodynamic data

Figure 1 shows the baseline systolic and peak recorded arterial pressure of each participant. A peak systolic arterial pressure of greater than 120% of baseline was recorded in four subjects (number 2, 3, 5 and 10), and an increase to greater than 130% was seen in one subject (number 7 from 110 to 144 mm Hg). The greatest rise was seen in subject number 15 where the systolic value rose to 195 mm Hg from a baseline of 133 mm Hg (147% of baseline). This figure was preceded and succeeded by two lower values of 136 mm Hg and 126 mm Hg respectively, suggesting a possible measurement artefact. Figure 2 shows the baseline and peak heart rate of each participant. A rise in heart rate to within 120% of baseline was seen in 10 cases (numbers 2, 4, 6, 7, 10, 11, 12, 13, 14 and 15), to over 130% in two (number 1 and 9), and to over 150% in one case (number 3).

ECG and oximetry

Continuous monitoring of the ECG and oxygen saturation failed to reveal any significant abnormality other than changes in heart rate. No treatment or intervention was required.

Table 1 Subjective response of participants to the overall experience of undergoing the procedure, pain felt during the procedure, anxiety felt during the procedure and coughing and gagging experienced during the procedure Since two of the subjects were instructors on the course, feed back forms were not collected from them

Overall experience		**Pain**		**Anxiety**		**Coughing/gagging**	
Very distressing	0	Very painful	0	Very worrying	0	Very uncomfortable	0
Distressing	0	Painful	0	Worrying	1	Uncomfortable	1
Acceptable	11	Slightly painful	6	Slightly worrying	6	Slightly uncomfortable	8
Enjoyable	2	Not at all painful	7	Not at all worrying	6	Not at all uncomfortable	4
Very enjoyable	0	Enjoyable	0	Enjoyable	0	Enjoyable	0
Total participants	13		13		13		13

Complications

Paraesthesia

One delegate complained of severe paraesthesia and numbness in the hands and feet prior to intubation. The procedure was abandoned, following which the tingling sensation settled over the next 20 min.

Nasal bleeding

Slight bleeding from the inferior turbinate was observed in two participants. Nasal bleeding caused no distress and settled without treatment. It did not interfere with endoscopy.

Coughing

All delegates coughed at some stage during the procedure. There were no episodes of laryngospasm or bronchospasm.

Sore throat

Two delegates recorded post-procedural sore throat; none reported voice changes.

Intubations

The carina was visualized in all 15 subjects; intubation was completed in 10. Nasal obstruction prevented nasotracheal intubation in three cases. Inadequate analgesia caused failure to intubate in one case and the procedure was abandoned in the one individual who developed paraesthesia of the hands and feet.

Subjective responses

All participants graded the overall experience as acceptable. The subjective responses are shown in Table 1. Seven participants (54%) experienced no pain during the procedure; six participants (46%) experienced slight pain. Anxiety was common and was experienced by seven participants (54%); six participants (46%) reported no anxiety. Coughing and gagging were rated as uncomfortable by one individual (7%), and slightly uncomfortable by eight (62%) participants; four participants (31%) reported no discomfort.

The course overall was rated as excellent by 100% of delegates, all of whom returned a completed evaluation form (Appendix D). Two reported that they found the experience of undergoing endoscopy beneficial, by aiding their recall of the technique and improving empathy when dealing with patients.

Discussion

No delegate found the procedure unacceptable. Reported levels of discomfort and anxiety were low. Only one participant found the procedure worrying and six participants found it slightly worrying (Table 1). However, a course of this kind could be predicted to select individuals most likely to find this type of procedure acceptable. The findings reported here may not therefore be reproduced from a cross-section of the population.

Heart rate and arterial pressure changes during a practical procedure may give an objective indication of the distress or discomfort produced. A rise in heart rate was seen in all individuals at some stage during the endoscopy. The average maximum rise in heart rate was 13 beat min^{-1}, which represented 120% of the baseline value. Part of this increase may be attributable to administration of glycopyrrolate. In line with the heart rate changes, systolic arterial pressure increased in all individuals at some stage during the procedure, although the average maximal rise was 21 mm Hg to 117% of the baseline value.

One individual complained of dizziness and paraesthesia, symptoms that could be attributed to lidocaine toxicity. However, we frequently ask individuals to breathe deeply at some point during the endoscopy to aid the distribution of local anaesthetic. It is possible, therefore, that these symptoms could also have been attributed to hyperventilation. The sensation of tingling and dizziness resolved within 20–30 min of discontinuing endoscopy, at a time when plasma lidocaine levels would be expected to be elevated or even rising.[7 8]

Endoscopy to visualize the carina was completed in all subjects, though nasal intubation was performed in only 66%. The main objective of the course is to provide training in airway local anaesthesia and fibreoptic endoscopy Many of the benefits of the course in developing endoscopy skills and learning local anaesthesia of the airway can be achieved without performing tracheal intubation. However, completion of the procedure allows the instructors to encourage gentleness, and gives the opportunity to demonstrate the manoeuvres sometimes required to assist the passage of the tracheal tube. Perhaps most importantly, when delegates are given the opportunity to complete the intubation, their confidence in the validity of the local anaesthetic technique is enhanced.

The assertion that intubation attempts were abandoned in the event of any apparent distress is supported by the low levels of discomfort and high level of acceptability reported by delegates. Nevertheless, all delegates witnessed the technique of tracheal tube insertion, even if they did not successfully perform it themselves.

In conclusion, the use of course delegates as subjects for training in fibreoptic endoscopy is acceptable to some anaesthetists. Early assessment suggests that this is associated with a low level of discomfort and morbidity. Delegates found this type of instruction beneficial.

Appendix A

Application forms for the observer and the participant on the Norwich Endoscopic Airway Training Course are given in Table 2.

Appendix B

The detailed subjective description of endoscopy and intubation is shown in Table 3.

Table 2 The Norwich Endoscopic Airway Training Course. Information required on the application forms for observers and participants

Application Form - Observer

Surname
First name
Sex
Address
Contact telephone numbers
Qualifications (with dates)
GMC registration number
Current grade
Current hospital
Level of experience in fibreoptic intubation (none/minimal/moderate/extensive)
Approximate number of fibreoptic intubations under general anaesthesia (under supervision/solo)
Approximate number of intubations under local anaesthesia (under supervision/solo)
What does the applicant hope to gain from this course?
If the course is oversubscribed would the applicant like to be offered a cancellation possibly at short notice?

Application Form - Participant

Surname
First name
Sex
Address
Contact telephone numbers
Qualifications (with dates)
GMC registration number
Current grade
Current hospital
Level of experience in fibreoptic intubation (none/minimal/moderate/extensive)
Approximate number of fibreoptic intubations under general anaesthesia (under supervision/solo)
Approximate number of intubations under local anaesthesia (under supervision/solo)
What does the applicant hope to gain from this course?
Weight of applicant in kg
Blood pressure of applicant in mm Hg
Resting pulse rate of applicant in beat/min
Does the applicant have any infectious diseases (such as Hepatitis B)?
Is the applicant on any medication other than the oral contraceptive pill?
Does the applicant suffer with any of the following:
  Hypertension
  Heart disease
  Liver disease
  Epilepsy
  Diabetes
  Asthma
Is the applicant pregnant?
A 'yes' answer to any of the above would mean the applicant could not become a participant
Any other current medical problems
Does the applicant suffer from nosebleeds?
List of all known allergies
Any history of nasal obstruction or nose problems
If the course is oversubscribed would the applicant like to be offered a cancellation possibly at short notice?

Table 3 Detailed subjective description of endoscopy and intubation

Intubation Under Local Anaesthetic! How safe is it?

Before volunteering for an awake intubation you will need to understand what is involved, the risks of the procedure and exactly how you can expect to feel during and afterwards.

This method of airway anaesthesia has been used repeatedly on patients, previous delegates and the instructors themselves, all of whom have undergone multiple tracheal intubations under local anaesthesia to refine their technique

Method

The procedure takes place in an operating theatre with full resuscitation facilities available.

After a 4-h fast you will be weighed and routine monitoring established This will be followed by topical xylometazoline (Otrivine) nose drops applied to both nostrils A 20/22-gauge cannula is inserted into the dorsum of the hand or the antecubital fossa, and glycopyrrolate 200–400 μg given intravenously Oxygen will be administered by nasal cannulae and followed by the topical application of lidocaine directly or as a fine spray throughout the airway via a fibreoptic scope. When satisfactory anaesthesia has been achieved and tested a 6.0 nasotracheal or orotracheal tube will be passed into the trachea Airway anaesthesia, endoscopy and intubation will be performed by course members under direct supervision of an experienced consultant Each delegate will perform part of the procedure on the subject, the last delegate will perform endoscopy and tracheal intubation. Pulse, BP and Sa_{O_2} will be monitored at frequent intervals during the procedure No local anaesthetic injections, cocaine or sedation will be used.

Risks

Trauma to the airway from nose to main bronchi including bleeding or perforation and abscess formation.

Allergic reactions to lidocaine, glycopyrrolate or phenylephrine

Drug toxicity due to lidocaine resulting in convulsions, myocardial depression or cardiac arrest.

Aspiration of gastric contents.

Infection: localized or systemic, due to hepatitis B, hepatitis C, HIV, TB, CJD and any other contaminating organisms.

With the exception of minor nasopharyngeal trauma, none of these complications has been observed during the preparatory stages Doses of lidocaine applied to the airway are large (up to 9 mg kg^{-1}). These have been found to be acceptable in patients undergoing bronchoscopy (Efthimiou J, Higenbottam T, Holt D, Cochrane GM Plasma concentrations of lignocaine during fibreoptic bronchoscopy *Thorax* 1982; **37** 68–71). Awake fibreoptic intubation has been reported to be safe in patients at risk of aspiration (Ovassapian A, Krejcie TC, Yelich SJ, Dykes MHM Awake fibreoptic intubation in patients at high risk of aspiration *Br J Anaesth* 1989; **62**· 13–16).

How does it feel?

There is obviously a degree of apprehension associated with anticipation of an awake intubation. We observe a 4-h fast before the procedure, but despite this it is advisable to ensure an empty bladder as the whole procedure may take an hour

You will be settled in the supine position with head elevated on a fairly comfortable operating table Monitoring will be applied – NIBP, ECG and pulse oximetry After a period of stabilisation to give you time to settle down a small cannula will be inserted into the back of your hand or the antecubital fossa, whichever you prefer Early preparation includes the application of a vasoconstrictor to the nose We use xylometazoline two squirts to each nostril, this is a little uncomfortable and sometimes makes the eyes water. This is followed by the i.v administration of glycopyrrolate 200–400 μg Over the following 10 min the glycopyrrolate will produce a dry mouth Nebulized 4% lidocaine is used to begin anaesthetising the upper airway This is followed by the application of co-phenylcaine forte (0 5% phenylephrine, 5% lidocaine and 0 001% benzalkonium spray) Topical application of local anaesthetic spray to the airway tastes unpleasant, as lidocaine has a bitter taste and produces coughing or gagging If the endoscope is advanced too early, before satisfactory anaesthesia has been achieved, this can cause swallowing coughing, gagging or retching

When the larynx ceases to react to further increments of local anaesthetic the tracheal tube is passed through the nose A small tube is used, through the largest nostril or through the mouth As it passes through the nose the subject may hear some clicking noise though this is uncommon In general, the procedure is well tolerated

The tracheal tube position is confirmed, then it is removed. The subject will feel a certain degree of elation when the procedure is over This sensation is enhanced by the effects of lidocaine which produces some dysphoria Following the procedure the subject will be aware of a dry mouth which outlasts the procedure by 2–3 h and of nasal stuffiness similar to that which occurs in the early stages of a cold. When oropharyngeal sensation returns to normal we recommend a warm cold-cure drink containing aspirin or paracetamol to deal with the nasal discomfort This usually settles after 12–14 h Other useful things to have available are a Lipsyl stick for the dry mouth and some Vicks vaporub, which eases nasal stuffiness overnight

Clearly in a course of this kind, it is essential that we exercise utmost caution For this reason we are explicit about the risks and some delegates will be refused entry as participants Participating delegates should not drive for 4 h after endoscopic intubation. Accommodation should be arranged locally following the course

If you need additional information, or have concerns about a medical condition or the practical aspects of the course, please contact us.

Appendix C

The participant consent form is given in Table 4.

Appendix D

The feedback questionnaire is shown in Table 5.

Table 4 Information taken from page 3 of the Participant Application Form

---

Consent to Intubation Under Local Anaesthesia

As a participant, the course will involve undergoing fibreoptic naso/orotracheal intubation under topical local anaesthesia. If you are unwilling to consent to this please apply for course attendance as an observer

Participants must not drive for 4 h after the procedure, therefore you must make arrangements to stay locally after the course

Morbidity

Inevitably there is some discomfort during the procedure, mainly airway irritation which causes coughing You should expect some post-procedural nasal stuffiness, lasting a few days and a dry mouth for 3–4 h

Risks of awake fibreoptic intubation under local anaesthesia include

Trauma anywhere within the airway

Allergic reaction to latex, xylometazoline, lidocaine, or glycopyrrolate.

Local anaesthetic toxicity, leading to convulsions or cardiac arrest

Aspiration of gastric contents.

Infections, local or systemic, due to hepatitis B, hepatitis C, HIV, TB, CJD and any other contaminating organisms

Any queries?

If you wish to discuss the course, or need further clarification, please contact our Course Administrator

---

All applicants wishing to participate in, rather than observe the course should complete the consent form below

Consent to Tracheal Intubation Under Local Anaesthesia

I wish to participate in the Norfolk and Norwich Endoscopic Airway Training Course and in doing so I am willing to act as a subject for tracheal intubation under topical local anaesthesia I am aware of the possible risks of the procedure and of the alternative option, which is to apply to join the course as an observer I am also aware that I must not drive a motor vehicle for at least four hours following the procedure

Please print your name ... ...

Signature . . . . Date .. . .

Your reaffirmation of consent will be sought at the time of training and you will be asked to sign the form below

Signature . ... Date ....

Table 5 Feedback questionnaire Participants are asked to complete the following questionnaire about the Norwich Endoscopic Airway Training Course before they leave at the end of the last day.

---

1) Were you an observer or participant?

2) What was your overall impression of the course? (circle one)

Very Poor / Poor / Fair / Good / Excellent

3) How did you find the experience of endoscopy or intubation on yourself? (circle one)

Very distressing / Distressing / Acceptable / Enjoyable / Very enjoyable

4) Considering different aspects of airway endoscopy or intubation on yourself, how would you rate the following categories? (circle one from each category)

Pain

Very painful / Painful / Slightly painful / Not painful at all / Enjoyable

Anxiety

Very worrying / Worrying / Slightly worrying / Not worrying at all / Enjoyable

Coughing / Gagging

Very uncomfortable / Uncomfortable / Slightly uncomfortable / Not uncomfortable at all / Enjoyable

Other sensation (Please specify)

Very uncomfortable / Uncomfortable / Slightly uncomfortable / Not uncomfortable at all / Enjoyable

5) If you experienced pain, anxiety, coughing / gagging or other sensations at what stage of the procedure did this happen?

a) Pain
b) Anxiety
c) Coughing / Gagging
d) Other sensation

6) Did you feel that you experienced any of the recognized side-effects of local anaesthetic drugs? Yes / No

If "Yes" please specify

At what stage did you experience these side-effects?

How were they resolved and was this adequate?

7) Is there any other information we could have supplied before the course that you would have liked or that you feel would have improved either the educational content or the experience of fibreoptic intubation?

8) What, do you feel, are the specific strengths and weaknesses of this course?

9) Why did you decide to come on this course (what objectives did you hope to fulfil)?

10) Do you feel that this course has met your objectives? (Please describe any areas that the course has failed to meet your objectives.)

11) Would you recommend this course to a colleague? Yes / No

If "Yes" why would you recommend it?

If "No" why would you not recommend it?

12) Are there any other comments you would like to add?

References

1 Mason RA. Learning fibreoptic intubation: fundamental problems. *Anaesthesia* 1992; **47**: 729–31

2 Williams K, Harwood R, Woodall N, Barker G. Training in fibreoptic anaesthesia. *Anaesthesia* 2000; **55**. 99

3 Woodcock A, Campbell I, Collins JV, *et al.* Bronchoscopy and infection control. *Lancet* 1989; 270–1

4 Watanabe H, Lindgren L, Rosenberg P, Randell T. Glycopyrronium prolongs topical anaesthesia of oral mucosa and enhances the absorption of lignocaine. *Br J Anaesth* 1993; **70**: 94–5

5 O'Hare D, Harwood R, Woodall N, Barker G. A method of administering topical anaesthesia for airway endoscopy. *Anaesthesia* 2000; **55**: 616

6 Efthimiou J, Higenbottam T, Holt D, Cochrane GM. Plasma concentration of lignocaine during fiberoptic bronchoscopy. *Thorax* 1982; **37**· 68–71

7 Bigeleisen PE, Schisler JQ, Finucane BT. Plasma lidocaine levels following transtracheal injection during topical anaesthesia of the upper airway. *Can J Anaesth* 1988; **35**. S95–6

8 Patterson JR, Blaschke TF, Kellog Hunt K Jr, Meffin PJ. Lidocaine blood concentrations during fiberoptic bronchoscopy. *Am Rev Respir Dis* 1975; **112**: 53–7

British Journal of Anaesthesia 89 (4). 594–8 (2002)

Evaluation of effects of magnesium sulphate in reducing intraoperative anaesthetic requirements

L. Telci[1], F. Esen[1]*, D. Akcora[1], T. Erden[1], A. T. Canbolat[2] and K. Akpir[1]

[1]Department of Anaesthesiology and Intensive Care, Faculty of Medicine, University of Istanbul, Istanbul, Turkey. [2]Department of Neurosurgery, Faculty of Medicine, University of Istanbul Istanbul, Turkey

**Corresponding author: Department of Anaesthesiology and Intensive Care, Faculty of Medicine, University of Istanbul, 34390 Capa Istanbul, Turkey*

Background. The present randomized, placebo-controlled, double-blind study was designed to assess the effect of peroperatively administered i.v. magnesium sulphate on anaesthetic and analgesic requirements during total i.v. anaesthesia.

Methods. Eighty-one patients (36 women, 45 men) undergoing elective spinal surgery were included in one of two parallel groups. The magnesium group received magnesium sulphate 30 mg kg^{-1} as a bolus before induction of anaesthesia and 10 mg kg^{-1} h^{-1} by continuous i.v. infusion during the operation period. The same volume of isotonic solution was administered to the control group. Anaesthesia was maintained with propofol (administered according to the bispectral index) and remifentanil (adjusted according to heart rate and arterial blood pressure) infusions.

Results. A significant reduction in hourly propofol consumption was observed with magnesium administration. For example, the mean infusion rate of propofol in the second hour of the operation was 7.09 mg kg^{-1} h^{-1} in the control group *vs* 4.35 mg kg^{-1} h^{-1} in the magnesium group ($P<0.001$). The magnesium group required significantly less remifentanil ($P<0.001$) and vecuronium ($P<0.001$). No side-effects were observed with magnesium administration.

Conclusion. The administration of magnesium led to a significant reduction in the requirements for anaesthetic drugs during total i.v. anaesthesia with propofol, remifentanil and vecuronium.

Br J Anaesth 2002; **89**: 594–8

Keywords: anaesthesia, i.v.; ions, magnesium

Accepted for publication: June 11, 2002

Magnesium is the fourth most abundant cation in the body and the second most abundant intracellular cation.[1 2] It activates many of the enzyme systems involved in energy metabolism and acts as a natural calcium antagonist by regulating calcium access into the cell.[3] Recently, the importance of magnesium in anaesthetic practice has been highlighted.[2] It has been suggested that magnesium has the potential to treat and prevent pain by acting as an antagonist of *N*-methyl-D-aspartate (NMDA) receptors.[4 5] In animals, magnesium suppressed NMDA-induced adverse behavioural reactions and hypersensitivity resulting from nerve injuries.[5] In a clinical study, the role of magnesium in reducing analgesic requirements during the postoperative period has been demonstrated.[6] Recently, Koinig and colleagues reported that magnesium administration led to a significant reduction in fentanyl consumption in the peri- and postoperative periods.[7]

At the beginning of the last century, magnesium sulphate was proposed as a general anaesthetic.[8 9] Although magnesium was regarded as a central nervous system (CNS) depressant, its anaesthetic effect was shown to result from cerebral hypoxia after progressive respiratory and cardiac depression. When respiratory support was maintained, patients showed no CNS depression even at very high serum concentrations of magnesium.[10] On the other hand, a 60% reduction in minimum alveolar concentration of

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

halothane was demonstrated in magnesium-treated rats. This result was ascribed to a central effect of the ion, but this has not been substantiated.[11]

The present randomized, placebo-controlled, double-blind study was designed to assess the effect of perioperatively administered i.v. magnesium sulphate on anaesthetic and analgesic requirements during total i.v. anaesthesia with propofol, remifentanil and vecuronium.

Methods

The study was approved by the ethics committee of Istanbul Faculty of Medicine and informed consent was obtained from each patient. Eighty-one ASA physical status I–II patients (36 women, 45 men) undergoing elective lumbar discectomy were included in one of two parallel groups (control, n=41; magnesium, n=40).

Exclusion criteria included major hepatic, renal or cardiovascular dysfunction, atrioventricular block, known allergy to magnesium sulphate or other study drugs, asthma, chronic obstructive pulmonary disease, haematological disorders, obesity, pregnancy and prior treatment with calcium channel blockers, opioids and anticoagulants. The patients were assigned randomly to one of the two groups. The magnesium group received 15% magnesium sulphate and the control group received 0.9% sodium chloride in a double-blind fashion. The solutions were prepared by the coordinator of the study, and the anaesthetist who was in charge of the patients during the operation was unaware of the study medication. Before the induction of anaesthesia, routine monitoring (ECG, pulse oximetry, oesophageal temperature) was started and an i.v. line was sited. An arterial line was inserted to measure systemic blood pressure with a Transpac i.v. system (Abbott Critical Care Systems, Abbott, Sligo, Ireland) on a Datex-Ohmeda AS/3 monitor (Datex-Ohmeda, Bromma, Sweden). Muscle relaxation was monitored with a neurotransmission module (M-NMT) incorporated into the Datex-Ohmeda AS/3 unit. The surface electrodes were positioned over the ulnar nerve at the wrist. The mechanosensor was attached between the thumb and index finger with a piece of tape and the forearm was wrapped in a cotton blanket to minimize cooling. The level of anaesthesia was monitored with the bispectral index (BIS™) method. The BIS electrodes were placed on the forehead and were connected to an A-2000 BIS monitoring system (Aspect Medical Systems, Framingham, MA, USA). A bispectral index of 40–60 was considered the target range for surgical anaesthesia.[12]

Study protocol

Standard recordings of heart rate, systemic pressure [mean arterial pressure (MAP)], arterial oxygen saturation (Sp_{O_2}) and BIS values were performed before the induction of anaesthesia. The magnesium group received magnesium sulphate 30 mg kg^{-1}, administered as a slow i.v. bolus before the induction of anaesthesia, and 10 mg kg h^{-1} by continuous i.v. infusion during the operation. The same volume of isotonic saline was administered to the control group. After preoxygenation of at least 2 min, anaesthesia was induced with fentanyl 1 μg kg^{-1} and propofol in increments of 20 mg every 5 s until the BIS reached a predetermined value of 60. After induction of anaesthesia, supramaximal train-of-four (TOF) stimulation was measured at 20 s intervals. When a stable twitch response (at least three successive equal responses to TOF stimulation) had been established, vecuronium 10 μg kg^{-1} was administered via a fast-flowing i.v. infusion over 5 s. The time from the start of anaesthesia induction to reaching a BIS of 60 and the time to 80% (T1=20%) single-twitch depression after administering vecuronium were recorded. Orotracheal intubation was performed after complete (T1=0%) single-twitch depression, then a further set of recordings was made.

Anaesthesia was maintained by propofol and remifentanil infusions. The propofol infusion was started at the rate of 10 mg kg^{-1} h^{-1} and titrated to maintain a BIS in the range 45–60. The hourly consumption of propofol was recorded as mg kg^{-1} h^{-1}. Dose adjustments of remifentanil were based on standard clinical signs and haemodynamic measurements. Signs of inadequate analgesia, defined as an increase in heart rate and mean arterial pressure of more than 20% of baseline, hypertension or hypotension (systolic arterial pressure <90 mm Hg) were to be managed with increased and decreased remifentanil respectively (if BIS was within the recommended range).[7] Muscle relaxation was achieved by vecuronium infusion adjusted to provide complete depression of the first twitch after TOF stimulation. Hourly infusion rates of remifentanil and vecuronium were recorded as μg kg h^{-1}.

The lungs of all patients were ventilated mechanically with an oxygen/air mixture to maintain adequate oxygenation and a Pa_{CO_2} level between 35 and 40 mmHg. Normothermia was maintained during the whole procedure.

Approximately 30 min before the end of surgery, the vecuronium infusion was discontinued. After discontinuation of the vecuronium infusion, the patients were allowed to recover spontaneously until the return of T1=25%. Then a combination of atropine 0.01 mg kg^{-1} i.v. and prostigmine 0.02 mg kg^{-1} was administered to reverse the neuromuscular block. The times for return of T1 to 25% and return of the TOF ratio (T4/T1) to 70% were recorded. Propofol was discontinued on skin closure and the patient was allowed to wake up. Patients were extubated when the BIS reached 80, and the time to BIS=80 was recorded as the recovery period.

Each patient was observed continuously after the termination of anaesthesia and times of events were recorded by the anaesthetist. After transfer to the recovery area, patients were assessed neurologically for any sign of hypermagnesaemia. Any adverse events or side-effects were recorded during the perioperative and postoperative periods

Statistical analyses

Comparisons between the control and the study groups were conducted using Student's *t* test, analysis of variance (ANOVA) or repeated measures ANOVA, as appropriate.

The analysis was conducted on an intention-to-treat basis. Data for missing values were evaluated by the last observation carried forward (LOCF) method. For LOCF analysis, the last measurement was carried forward into all subsequent time slots for which actual measurements were not available. A P value below 0.05 was considered significant.

Results

The groups were comparable with respect to age, weight, ASA status and duration of surgery. All patients underwent the same type of surgery (discectomy), performed by the same group of surgeons. The numbers of cases in the control and magnesium groups respectively, according to operation duration, were as follows: 1–5 h, 27 and 27; up to 6 h, 3 and 6; up to 7 h, 5 and 2; up to 8 h, 4 and 3; up to 9 h, 2 and 2 patients.

In neither measurement period was there any statistically significant difference in heart rate or arterial blood pressure between the two groups. No haemodynamic instability was observed with magnesium perfusion during the observation period.

Induction of anaesthesia (BIS=60) was achieved in 55.4 (SD 10.6) s in the magnesium group and in 81.2 (13.6) s in the control group ($P<0.0001$). The recovery time was shorter in the control group (7.19 *vs* 9.60 min, $P<0.0001$). The baseline mean BIS before induction was above 90% for both the study and the control group. After induction, the mean BIS value, calculated from the lowest of the BIS values that were recorded every hour during the operational period, was not different between the two groups (Fig. 1). The times from the cessation of vecuronium to T1=25% (48.08 *vs* 38.73 min, $P<0.001$) and T4/T1⩾70% (51.70 *vs* 41.59 min, $P<0.001$) were significantly longer in the magnesium group compared with the control group.

The mean anaesthetic requirements, measured every hour and evaluated by the LOCF method, are given in Table 1. Significantly lower propofol, remifentanil and vecuronium requirements were recorded during each measurement period in the magnesium group. When the hourly consumption rates of each drug were evaluated within the groups, significant reductions were observed in the second and third hours for propofol and remifentanil consumption in both groups. For vecuronium, a significant dose reduction was only apparent in the magnesium group.

Discussion

We studied the possible effects of magnesium sulphate in reducing the anaesthetic requirements during total i.v. anaesthesia with propofol, remifentanil and vecuronium. Our results demonstrate a significant reduction in the consumption of each drug used for balanced anaesthesia with magnesium administration. To our knowledge, this is the first study evaluating the potentiating interaction of magnesium with a combination of analgesic, hypnotic and muscle relaxant.

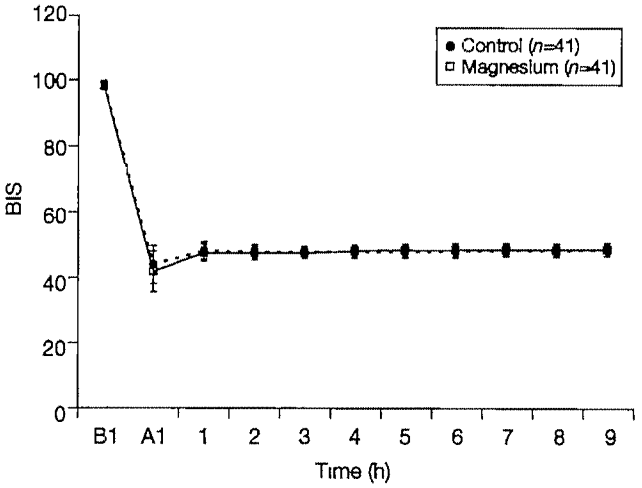


Fig 1 Bispectral index (BIS) levels. Plot of BIS (mean±SD) against time from induction to the end of surgery. BI=before induction; AI=after induction.

Importantly, we used an objective, quantitative measure of the anaesthetic state (BIS) to guide anaesthetic requirements[13–16] and to determine end-points. Induction of anaesthesia with propofol was more rapid in the presence of magnesium, but recovery was slower. The effects of magnesium on propofol consumption could be related to a sedative effect of magnesium, but evidence for such an effect is conflicting. Magnesium has been reported to produce general anaesthesia and enhance the activity of local anaesthetic agents.[17] [18] In these studies, depressant effects on the CNS of animals injected with magnesium salts were reported. A narcotic state in human beings undergoing surgical operations was achieved in a study by Peck and Meltzer, who reported three patients undergoing hernioraphy under attempted anaesthesia by magnesium sulphate infusion.[9] However, Aldrete and colleagues suggested that this anaesthetic state was actually a sleep-like state caused by cerebral hypoxia from progressive respiratory and cardiac depression.[19] When ventilation was maintained, even very high levels of serum magnesium produced no CNS depression.[11] In healthy volunteers, i.v. magnesium failed to induce sleep even at magnesium concentrations 10 times higher than normal. The subjects felt and heard everything happening up to when the magnesium level exceeded 7 mmol litre^{-1}. There were no signs of anaesthesia, but the hand-grip force was markedly reduced.[10] On the contrary, increasing the magnesium dose was found to be associated with reductions in halothane

Table 1 Propofol, remifentanil and vecuronium consumption during maintenance of total i v. anaesthesia P values were determined by comparing control and magnesium groups *Significant difference within group (*P*<0 05)

	Hours								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Propofol (mg kg^{-1} h^{-1})									
Control (*n*=41)	8.91 (0.84)	7 09 (1 19)*	6.88 (0 99)*	7 04 (0 66)	7 25 (0 79)	7 26 (0 77)	7 33 (0 88)	7 52 (0 37)	7.9 (0 14)
Magnesium (*n*=40)	8.23 (1 27)*	4 35 (0 64)*	3 52 (0 35)*	3 59 (0.29)	3 64 (0.22)	3.65 (0 12)	3 83 (0 16)	3 92 (0 13)	3 75 (0 07)
P	0 006	<0 001	<0.001	<0 001	<0 001	<0.001	<0 001	<0 001	0 004
Remifentanil (µg kg^{-1} h^{-1})									
Control (*n*=41)	9 35 (1.6)2*	6 33 (1 39)*	5.82 (0 93)*	5 58 (0.89)	5.90 (0.77)	5.68 (0 57)	5 58 (0 97)	5 58 (0 97)	5 75 (0 35)
Magnesium (*n*=40)	4 74 (1.16)*	2 65 (0 59)*	2 17 (0 29)*	2 08 (0 19)	2.27 (0.32)	2 86 (0.26)	2 28 (0 26)	2 08 (0 20)	2 (0)
P	<0 001	<0 001	<0 001	<0 001	<0 001	<0 001	<0 001	<0 001	0 042
Vecuronium (µg kg^{-1} h^{-1})									
Control (*n*=41)	37 25 (7 24)	32 (11 97)	36 96 (8.75)	38 75 (8.25)	36 25 (8 85)	31 (7 12)	30 63 (9 30)	27 5 (13 69)	21.25 (1 76)
Magnesium (*n*=40)	20.88 (2 74)*	15 75 (3 87)*	14.23 (3 01)*	14 79 (3 63)	12 86 (3.97)	12.12 (3.36)	13 93 (2 83)	10 42 (3 68)	7 5 (0)
P	<0 001	<0 001	<0 001	<0 001	<0 001	<0.001	<0 001	0 027	0 058

MAC in rats.[11] With these data, Thomson and colleagues[11] suggested that anaesthetics be titrated carefully in patients with high serum magnesium concentrations and patients receiving magnesium.

In the present study, the aim was not to evaluate magnesium as an anaesthetic agent but to find out if magnesium could reduce propofol requirements during general anaesthesia It is hard to speculate on the exact mechanism of magnesium's contribution to anaesthesia in our study. Theoretically, magnesium could modulate anaesthesia by several mechanisms. Magnesium antagonizes NMDA receptors in the CNS.[5] Another mechanism could involve the reduction of catecholamine release through sympathetic stimulation, by which magnesium might decrease peripheral nociceptor sensitization or the stress response to surgery.[16] However, these mechanisms do not explain the reduction in propofol requirements independently of the reduction in requirements for remifentanil. Clearly, further studies of the interaction between magnesium and propofol as a sole agent are needed.

Our data demonstrated a significant reduction in remifentanil and vecuronium consumption during i.v. anaesthesia with continuous magnesium administration. The effect on vecuronium consumption is not surprising as the effects of magnesium ions at the neuromuscular junction are well known. The analgesic effect of magnesium has been demonstrated in several animal[4 5] and human[6 7] studies. The effect of magnesium on perioperative analgesic requirements was first evaluated by Koinig and colleagues in patients with identical levels of surgical stimulation.[7] Their data demonstrated that magnesium can be an adjuvant to peroperative analgesic management by lowering the fentanyl requirement. Recently, in a study by Shulz-Stübner and colleagues,[22] magnesium sulphate given as a bolus after induction produced a significant reduction in remifentanil and mivacurium consumption during general anaesthesia.

In our study, as in previous reports, the remifentanil requirement was adjusted according to haemodynamic changes as surrogate measures of intraoperative nociception. This might be considered a limitation of the study, as heart rate and MAP could change for many other reasons Also, magnesium inhibits the release of catecholamines and might blunt the haemodynamic responses to inadequate analgesia. These anti-adrenergic actions have led to the use of magnesium during surgery for phaeochromocytoma[23] and to evaluation of its efficacy in attenuating the response to endotracheal intubation.[24] However, the doses used in these studies, either as a bolus or as a perfusion, were twice as high as the dose we used in our study. As a matter of fact, our study population was ASA I–II patients in whom heart rate and MAP increases are probably caused by pain perception.

Unfortunately, we did not measure serum magnesium concentrations. However, it is known that the plasma magnesium concentration does not represent the magnesium content of the tissues. The lack of correlation between plasma magnesium and total body magnesium content in healthy subjects is also well recognized.[25] Arnold and colleagues showed that the measurement of intra- and extracellular magnesium concentrations does not predict magnesium levels in other body tissues accurately.[26] Doses of magnesium similar to ours were shown to produce reductions in analgesic requirements both during and after surgical interventions.[7] The dose–response relationship for magnesium with respect to its potentiating effect during balanced anaesthesia needs to be evaluated further.

In conclusion, the administration of magnesium led to a significant reduction in the amounts of anaesthetic drugs used during total i.v. anaesthesia.

References

1 Fawcett WJ, Haxby EJ, Male DA Magnesium· physiology and pharmacology *Br J Anaesth* 1999, **83**. 302–20

2 James MFM. Clinical use of magnesium infusions in anesthesia *Anesth Analg* 1992; **74**: 129–36

3 Iseri LT, French JH. Magnesium. nature's physiologic calcium blocker. *Am Heart J* 1984, **108**: 188–93

4 Feria M, Abad F, Sanchez A, Abreu P. Magnesium sulphate injected subcutaneously suppresses autonomy in peripherally deafferented rats. *Pain* 1993; **53**: 287–93

5 Woolf CJ, Thompson SWN. The induction and maintenance of central sensitization is dependent on *N*-methyl-D-aspartic acid receptor activation: implications for the treatment of post injury pain and hypersensitivity states. *Pain* 1991, **44**: 293–99

6 Tramer MR, Schneider J, Marti RA, Rifat K. Role of magnesium sulfate in postoperative analgesia. *Anesthesiology* 1996; **84**: 340–7

7 Koinig H, Wallner T, Marhofer P, Andel H, Horauf K, Mayer N. Magnesium sulfate reduces intra and postoperative analgesic requirements. *Anesth Analg* 1988; **87**: 206–10

8 Meltzer SJ, Auer J. Physiological and pharmacological studies on magnesium salts. II The toxicity of intravenous injection; in particular the effects upon the centers of the medulla. *Am J Physiol* 1906, **15**· 387–405

9 Peck CH, Meltzer SJ Anesthesia in human beings by intravenous injection of magnesium sulphate. *JAMA* 1916, **67**: 1131–3

10 Somjen G, Hilmy M, Stephen CR. Failure to anesthetize human subjects by intravenous administration of magnesium sulfate. *Pharmacol Ther* 1966, **154**· 652–9

11 Thompson SW, Moscicki JC, DiFazio CA. The anesthetic contribution of magnesium sulphate and ritodrine hydrochloride in rats. *Anesth Analg* 1988; **20**: 1273–5

12 Flashion R, Windsor A, Sebel PS. Recovery of consciousness after thiopental or propofol *Anesthesiology* 1997; **86**: 613–9

13 Lui J, Singh H, White PF. Electroencephalographic bispectral index correlates with intraoperative recall and depth of propofol induced sedation. *Anesth Analg* 1997; **84**· 185–9

14 Vernon J, Lang E, Sebel P, Manberg P. Prediction of movement using BIS electroencephalographic analysis during propofol/alfentanil or isoflurane/alfentanil anesthesia. *Anesth Analg* 1997, **80**· 780–5

15 Glass PSA, Bloom M, Kearse L, Rosow C, Sebel P, Manberg P. Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. *Anesthesiology* 1997; **86**: 836–47

16 Gan TJ, Glass PS, Windsor A *et al.* and the BIS Utility Study Group. Bispectral index monitoring allows faster emergence and improved recovery from propofol, alfentanil, and nitrous oxide anesthesia. *Anesthesiology* 1997; **87** 808–15

17 Meltzer SJ, Auer J. Physiological and pharmacological studies on magnesium salts. II Narcotizing effects of magnesium salts upon nerve fibers *Am J Physiol* 1906; **16**: 233–8

18 Countinho EM. Calcium, magnesium and local anesthesia. *J Gen Physiol* 1966; **49**: 845–6

19 Aldrete AJ, Barnes DR, Aikawa K. Does magnesium produce anesthesia? Evaluation of its effects on the cardiovascular and neurologic systems. *Anesth Analg* 1968; **47**: 428–33

20 Kehlet H. Postoperative pain relief—what is the issue? [editorial]. *Br J Anaesth* 1994; **72**: 375–8

21 Wilder-Smith OHG, Arendt-Neilsen L, Gäumann D, Tassonyi E, Rifat KR. Sensory changes and pain after abdominal hysterectomy: a comparison of anesthetic supplementation with fentanyl versus magnesium or ketamine. *Anesth Analg* 1998; **86**: 95–101

22 Shulz-Stubner S, Wettmann G, Reyle-Hahn SM, Rossaint R. Magnesium as part of balanced general anaesthesia with propofol, remifentanil and mivacurium: a double-blind, randomized prospective study in 50 patients. *Eur J Anaesthesiol* 2001; **18**: 723–9

23 James MFM. Use of magnesium sulphate in anesthetic management of phaeochromocytoma: a review of 17 anaesthetics. *Br J Anaesth* 1989; **62**: 616–23

24 James MFM, Beer RE, Esser JD. Intravenous magnesium sulphate inhibits catecholamine release associated with tracheal intubation. *Anesth Analg* 1989; **68**: 772–6

25 Dyckner T, Wester PO. Magnesium deficiency. Guidelines for diagnosis and substitution therapy. *Acta Med Scand* 1982; **661** (Suppl 1): 37–41

26 Arnold A, Tovey P, Mangat P, Penny W, Jacobs S. Magnesium deficiency in critically ill patients. *Anaesthesia* 1995; **50**: 203–5

British Journal of Anaesthesia 89 (4): 599–604 (2002) BJA

LABORATORY INVESTIGATIONS

Haemodynamic effects of an angiotensin-converting enzyme inhibitor and angiotensin receptor antagonist during hypovolaemia in the anaesthetized pig

F. Ryckwaert[1 2*], P. Colson[1 2], E. André[1], P.-F. Perrigault[1], G. Guillon[2] and C. Barberis[2]

[1]Faculté de Médecine, Université-Montpellier I, Montpellier, France. [2]INSERM U 469, Montpellier, France
**Corresponding author: Service d'anesthésie-réanimation, Hôpital Arnaud de Villeneuve, Avenue du Doyen Giraud, F-34295 Montpellier, France*

Background. Renin–angiotensin system antagonists, either angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor (AT_1) antagonists, may interfere with regulation of arterial pressure during anaesthesia. This study aimed to compare the haemodynamic profile of anaesthetized pigs, which were subjected to haemorrhage in the presence of the ACE inhibitor enalaprilat or the AT_1 antagonist valsartan.

Methods. Thirty-six pigs were assigned randomly to placebo, enalaprilat or valsartan groups. After a 30-min period of stabilization following anaesthesia and injection of the study drug, the animals were bled in two equal steps of 20% of their estimated blood volume (20% BV and 40% BV).

Results. After bleeding of 20% BV, the mean arterial pressure (MAP) decreased significantly but similarly in each group (20–25%) but the placebo and the enalaprilat groups had a significant decrease in cardiac index (CI, 22% and 16%, respectively) without significant change in systemic vascular resistance (SVR). Conversely, in the valsartan group, SVR decreased significantly (23%, $P<0.02$ *vs* other groups) without significant change in CI (–4%). After bleeding of 40% BV, the CI decreased significantly compared with 20% BV in the three groups (19% in the placebo and enalaprilat groups, 14% in the valsartan group) but the MAP decreased significantly in the enalaprilat group only (23%). The SVR increased significantly in the placebo group ($P<0.01$ *vs* each of the other groups), but there were no differences in the change in SVR between the other groups.

Conclusion. Blockade of the renin–angiotensin system by either enalaprilat or valsartan leads to a similar decrease in arterial pressure during anaesthesia and haemorrhage but the haemodynamic profiles are quite different.

Br J Anaesth 2002; **89**: 599–604

Keywords: arterial pressure, hypertension; complications, hypervolaemia; enzymes, angiotensin-converting enzyme, inhibition; model, pig; hormones, renin

Accepted for publication: May 15, 2002

Renin–angiotensin system (RAS) antagonists, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor (AT) antagonists, are increasingly used in the treatment of cardiovascular and other diseases.[1 2] Because angiotensin II is involved in short-term regulation of arterial pressure, the blockade of its effect by inhibition of either angiotensin II production (ACE inhibitor) or the AT-receptor-mediated effect (AT antagonist) may interfere with arterial pressure regulation.[3–6] During anaesthesia and surgery, arterial pressure may become angiotensin dependent.[7] The anaesthesia-induced reduction in sympathetic tone may be counterbalanced by angiotensin II,

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

especially when a reduction in intravascular volume is involved.[8] Accordingly, arterial pressure may decrease markedly during general anaesthesia when angiotensin II action is impeded by an angiotensin II competitive inhibitor.[9–11]

Much of the information regarding the physiology and pathophysiology of the renin–angiotensin system during anaesthesia and surgery has been based on studies of ACE inhibitors. Many cardiovascular effects are shared by ACE inhibitors and AT antagonists, and this is particularly true with regard to the short-term actions of angiotensin II on arterial pressure regulation. ACE is a non-specific carboxypeptidase involved in the conversion of angiotensin I to angiotensin II and in the inactivation of central opioids, enkephalins and bradykinin, a potent vasodilator. Inactivation of angiotensin II formation is, nevertheless, accepted to be the main mechanism of ACE inhibition.[1] AT antagonists have potential therapeutic interest:[2] first, they should not induce the bradykinin-related side-effects of ACE inhibitors, such as cough, which occurs in 10–20% of patients receiving ACE inhibitors. Secondly, because they competitively block specific receptors (AT_1), AT antagonists should suppress angiotensin II effects better than ACE inhibitors. Indeed, blockade of the converting enzyme favours other metabolic pathways leading to angiotensin II synthesis, especially the chymase pathway. However, the real importance of such converting-enzyme-independent angiotensin II synthesis is not well known. In addition, because the reduction in bradykinin breakdown caused by ACE inhibitors could participate in their therapeutic effect, AT antagonists may not provide a similar therapeutic profile. However, during AT_1 blockade, AT_2 receptors remain exposed to increasing levels of angiotensin II which could be a source of synergistic effects, as activation of AT_2 receptors has the opposite effect to activation of AT_1 receptors. Hence, stimulation of AT_2 receptors by increasing levels of angiotensin synergistically augments the effects of AT_1 receptor blockade.[6 12] Thus, the differences between ACE inhibitors and AT antagonists in the blockade of the renin–angiotensin system might lead to some haemodynamic consequences following stimulation of the renin–angiotensin system.

Clinical recommendations for the treatment of hypotensive episodes after induction of anaesthesia do not discriminate between ACE inhibitors and AT antagonists any more than they ascertain the role of changes in either cardiac output (CO) or vascular resistance (VR) in the mechanisms of hypotension.[9 11 13] Therefore, in an attempt to reveal differences between the two treatments, we compared the haemodynamic profile of anaesthetized pigs subjected to haemorrhage, and therefore dependent on the renin–angiotensin system for maintenance of arterial pressure, in the presence of a non-specific blockade of renin–angiotensin system with an ACE inhibitor and in the presence of a specific blockade of AT_1 receptors.

Materials and methods

Animals and preparation

Experiments were performed on female commercial farm-bred piglets (2–3 months, 15–22 kg). The study was approved by the Animal Care and Use Committee of our institution.

The animals were fasted except for water *ad libitum* for 12 h before induction of anaesthesia. The animals were premedicated with i.m. ketamine 20 mg kg^{-1}, midazolam 0.5 mg kg^{-1} and atropine 2 mg. An i.v. catheter was placed in an ear vein and lactated Ringer's solution was infused at a rate of 1 ml kg^{-1} h^{-1} using an i.v. infusion pump. Anaesthesia was induced with thiopental 2–3 mg kg^{-1}. The animal's trachea was intubated and the lungs ventilated mechanically with 1% isoflurane in 100% oxygen, keeping the end-tidal isoflurane concentration at 0.8–1.0 MAC and the end-tidal carbon dioxide pressure between 35 and 40 mm Hg (Datex Lab., Ultima).

A branch of the external carotid artery was cannulated to measure mean arterial pressure (MAP). A thermodilution pulmonary artery catheter was placed via a jugular vein to measure the central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP). CO was determined by thermodilution using a separate central venous injection catheter, as the average of three consecutive measurements. Cardiac index (CI), indexed stroke volume (iSV) and indexed systemic VR (iSVR) were calculated using the following formulae:

CI = CO/body weight (ml kg^{-1})
iSV = CI/heart rate (ml kg^{-1})
iSVR = (MAP–CVP)/CI (IU kg)

Temperature was measured in the pulmonary artery and was maintained using a heating blanket. After surgical preparation, piglets were allowed to stabilise for 30 min. At the end of the stabilization period, baseline measurements of heart rate (HR), MAP, PCWP, CI, iSV and iSVR were performed. At this time, the animals were assigned to the study groups.

Animal groups and experimentation

Preliminary studies

First, two animals were studied without any haemorrhage or injection protocol in order to estimate the potential drift effect over the time of the study experiment. No significant fluctuation was seen during the 90-min procedure. The maximum variation was less than 10% at any time for any variable: 7% for MAP, 1% for HR, 3% for CI and 7% for iSVR.

Second, the efficacy of the renin–angiotensin system blockade with either the AT_1 antagonist valsartan (Novartis Pharma, Basle, Switzerland) or the ACE inhibitor enalaprilat (Merck Sharp Dohme Chibret Laboratory, Paris, France) had been assessed through the inhibition of the agonist-induced increase in MAP. The agonists were angiotensin II and angiotensin I for enalaprilat and valsartan respectively, at a dose that increased MAP by at least 20%. We expected inhibition of the angiotensin-induced increase in MAP 90 min after the injection of the renin–angiotensin system blocker (which was the time required for the whole procedure) to be at least 50%. At a dose of 0.06 mg kg^{-1}, the inhibitory effect of enalaprilat on the arterial pressure response to injection of angiotensin I was 84%, 90%, 67% and 57% at 30, 60, 90, 120 min after the injection, respectively. Similarly the inhibitory effect of valsartan 3 mg kg^{-1} on the arterial pressure response to injection of angiotensin II was 75%, 56%, 50% and 43% at 30, 60, 90 and 120 min after the injection, respectively.

Study protocol

Thirty-six animals were assigned randomly to placebo, enalaprilat or valsartan groups. Injection consisted of a 10 ml sodium chloride solution for the placebo. Enalaprilat 0.06 mg kg^{-1} was dissolved in 10 ml sodium chloride solution, and valsartan 3 mg kg^{-1} in 10 ml distilled water. The piglets were allowed to stabilize for a 30-min period before being bled in two equal steps. Twenty percent of the calculated blood volume (BV) (based on a BV of 70 ml kg^{-1}) was removed over a 5-min period for each step.

Measurements consisted of HR, MAP, PCWP, CI, iSV and iSVR. After injection and after each stepped bleed, the animals were allowed to stabilize for 30 min and then measurements were collected 30 min after the injection and 30 min after each of the bleeds.

At the end of the experiment, the animals were killed with a central venous bolus injection of potassium chloride 40 mmol during deepened anaesthesia (MAC 2%).

Statistical analysis

Results are expressed as median [25%, 75% interquartile range] because some data were not normally distributed. Overall effects were evaluated by the Friedman test (within group) and Kruskal–Wallis analysis of variance (between groups). In the case of significant differences, further comparisons were made using Wilcoxon (within group) and Mann–Whitney *U* (between groups) tests. A value of $P<0.05$ was considered significant but the Bonferroni–Dunn procedure was used for correction of multiple comparisons when appropriate. A post-hoc power estimate (PHPE) with a confidence interval of 95% was performed when a statistically significant difference was observed between groups.

Results

The 36 animals were assigned randomly as follows: 13 placebo, 11 enalaprilat and 12 valsartan. Baseline values for HR, MAP, PCWP, iSVR, CI, and iSV are shown in Table 1. The end-tidal isoflurane concentration was 0.95% [0.8, 1.1] with no significant variation between groups or periods of measurement.

Effects of injection

Injections of placebo, enalaprilat or valsartan had no significant effect on MAP, PCWP, iSVR, CI and iSV. The haemodynamic profile was similar in each group, except for HR which after injection of valsartan decreased by 8% [3, 14] from baseline (P=0.022).

Effects of 20% BV haemorrhage (Fig. 1)

At the first bleed (20% BV), decreases in MAP from baseline were: 25% [21, 29] (P=0.002), 22% [19, 35] (P=0.003) and 25% [8, 33] (P=0.005) for the placebo, enalaprilat and valsartan groups, respectively. No significant difference was found between groups.

The decrease in MAP was associated with a decrease in CI in the placebo and enalaprilat groups: 22% [10, 29] (P=0.002) and 16% [4, 21] (P=0.005), respectively, and a decrease in iSVR in the valsartan group (23% [15, 28]) (P=0.002).

In the valsartan group, changes in CI and iSV from baseline were not statistically significant (–4% [+6, –15], and 1.0% [+6.8, +1.2], respectively), but were significantly different from changes in the placebo group ($P\leq0.014$, PHPE>0.90). The changes in iSVR were not significant in the placebo or enalaprilat groups, but were in the valsartan group ($P\leq0.016$, PHPE>0.60). Changes in HR were not statistically significant in any group.

Effects of 40% BV haemorrhage (Fig. 1)

Thirty min after the second bleed (40% BV), decreases in MAP from baseline in the placebo, enalaprilat and valsartan

Table 1 Haemodynamic data at baseline Values represent median (interquartile range)

Baseline data	**Placebo**	**Enalaprilat**	**Valsartan**
Heart rate (beats min^{-1})	106 (100–124)	107 (100–120)	106 (96–120)
Mean arterial pressure (mm Hg)	84 (75–89)	80 (67–84)	85 (73–91)
Pulmonary wedge pressure (mm Hg)	7 (6–8)	6 (5–8)	10 (6–12)
Cardiac index (ml kg^{-1})	115 (108–139)	114 (94–140)	107 (89–124)
Systemic vascular resistance (UI kg)	625 (549–709)	614 (569–743)	656 (568–814)
Indexed stroke volume (ml kg^{-1})	1.1 (0.9–1.4)	1.1 (0.9–1.2)	1.1 (0.8–1.2)

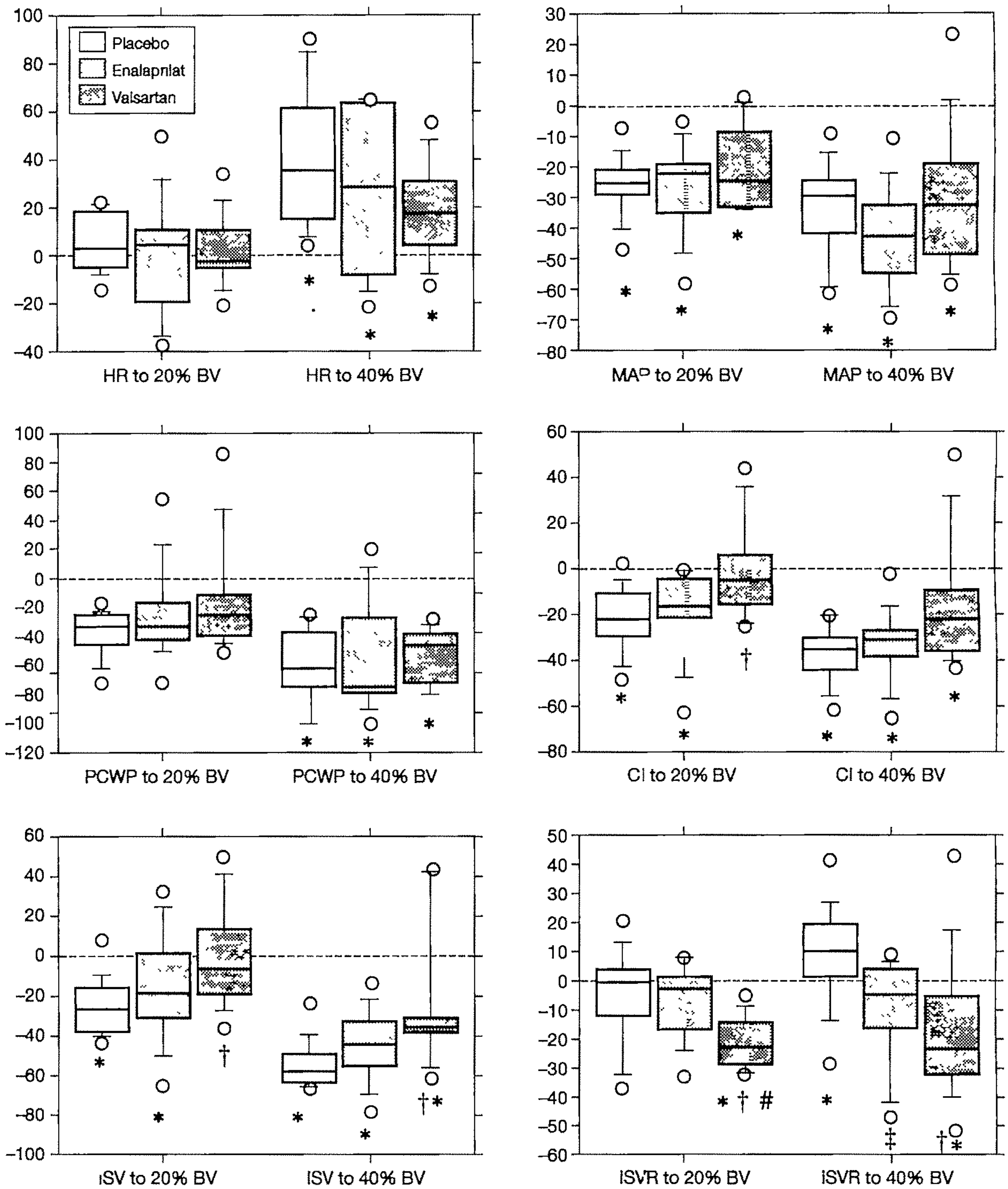


Fig 1 Changes (%) from baseline (T0) in heart rate (HR), mean arterial pressure (MAP), pulmonary capillary wedge pressure (PCWP), cardiac index (CI), indexed stroke volume (iSV) and indexed systemic vascular resistances (iSVR) changes after the first (20% BV) and second (40% BV) bleed in the three groups. Data are presented as median, interquartile range (boxes), 10–90% percentiles (bars), and range (circles). Values were compared within groups using a Friedman test then a Wilcoxon test $^{*}P\leq0.02$ from baseline. Values were compared between groups using a Kruskal–Wallis analysis of variance ($P\leq0.015$) then a Mann–Witney U test: $^{\dagger}P<0.015$ between the valsartan and placebo groups; $^{\#}P=0.016$ between the valsartan and enalaprilat groups, $^{\ddagger}P=0.01$ between the enalaprilat and placebo groups

groups were 29% [24, 41] (P=0.002), 43% [32, 54] (P=0.003) and 32% [19, 48] (P=0.005), respectively. The MAP decreased significantly from the 20% BV haemorrhage in the enalaprilat group only (23% [17, 28]) (P=0.005). No significant difference in the decrease in MAP was found between the groups (P=0.203).

The decrease in MAP was associated with a significant decrease in CI and iSV from baseline in all groups but the decrease in iSV was significantly lower in the valsartan group than in the placebo group (*P*=0.002, PHPE>0.95).

The changes in iSVR from baseline were significantly different between the placebo (+10.3% [+1.2, +19.4]) and valsartan groups (−23.3 [−40.2, −5.1]) (*P*=0.006, PHPE>0.85) and between the placebo and enalaprilat groups (−4.7% [−16.4, +3.4]) (*P*=0.010, PHPE>0.65) as a result of an increase in iSVR from the first bleed in the placebo group by 12% [2, 20] (*P*=0.007), while no significant change was found in the enalaprilat and valsartan groups (1.9% [−7.3, 3.3], −2.1% [−11.9, +23.9], respectively).

The increase in HR from baseline was 35% [15, 61] (*P*=0.002), 28% [−8, +63] (*P*=0.047) and 18% [+4, +31] (*P*=0.012) for the placebo, enalaprilat and valsartan groups, respectively. No significant difference in the increase in HR was found between groups (*P*=0.221).

Discussion

Although MAP appeared to be influenced similarly by both treatments during anaesthesia and hypovolaemia, the results show that renin–angiotensin system antagonists interfere with the haemodynamic determinants of arterial pressure (i.e. CO and VR) in quite different ways. While the ACE inhibitor induced a proportional decrease in MAP and CO, selective AT_1 blockade was associated with a vasodilatation and a preservation of CO and SV.

It is well accepted that, in conscious mammals, a moderate reduction (20–30%) in BV has little effect on MAP (less than 10% reduction), which is completely unaffected by inhibition or blockade of the combined effects of the two major hormones, angiotensin and vasopressin.[14 15] In the present study, the first haemorrhage (20% BV) induced a 20–25% decrease in MAP in all three groups. This important fall in MAP, larger than described in previous studies,[14 15] can be related to anaesthesia. Below 20–30% blood loss, the carotid sinus reflex control should have maintained MAP,[14 15] but under anaesthesia the baroreflex is blunted.[16] Even in the placebo group, the MAP decrease is 25% while the HR increased by 5%, suggesting that the slope of the baroreflex response to change in carotid sinus pressure is decreased. In anaesthetized animals, the arterial pressure is more sensitive to haemorrhage because of autonomic blockade.[17 18]

During anaesthesia and before bleeding, injection of placebo, enalaprilat or valsartan had no effect on MAP, which indicates that maintenance of arterial pressure is not dependent on the renin–angiotensin system.[7] After loss of 20% BV, MAP decreased similarly in the three groups (20–25%). Moreover the MAP, HR, CI and iSVR varied in the same way in the enalaprilat and placebo groups. The absence of vasoconstriction and the lack of significant differences between the enalaprilat and placebo groups in their haemodynamic profile may suggest that the renin–angiotensin system is not stimulated. However, the haemodynamic profile is completely different in the valsartan group: the MAP decrease is explained by the decrease in VR while CO and SV are unaffected. The 'paradoxical' vasodilatation observed when AT_1 is blocked in the context of haemorrhage suggests that the renin–angiotensin system is indeed activated. With selective AT_1 blockade, angiotensin, released in response to the hypovolaemia-induced stimulation of the renin–angiotensin system, may be available to activate AT_2. There is some evidence that angiotensin can act to physiologically antagonize its own hypertensive effects by causing relaxation of some vascular beds.[6 12] Activation of AT_2 has been proposed to counteract the effects of the AT_1 subtype [19] Scheuer and Perrone have demonstrated, in anaesthetized rats using AT_1 and AT_2 antagonists, that the AT_2 receptor mediates a vasorelaxation response to angiotensin.[20] Furthermore, the counteracting effects of AT_1 and AT_2 could account for the lack of effect in the placebo group. Nevertheless, a greater angiotensin level in the valsartan group cannot be ruled out, because selective AT_1 blockade decreases the angiotensin-induced feedback regulation of renin release.[21–23]

The involvement of the renin–angiotensin system in control of arterial pressure is even more apparent at the second haemorrhage (40% BV). In the control group, although the decrease in MAP from baseline is 30%, the iSVR increases about 12% from the 20%-BV bleed, suggesting the involvement of a vasoconstrictor system. By contrast, in the enalaprilat group the overall decrease in MAP is 40% as a result of a similar decline between baseline and 20% BV, and between 20% BV and 40% BV, and the iSVR does not increase. Both results suggest a prominent role of angiotensin in the vasoconstrictor response in the placebo group.

In the enalaprilat group the decrease in arterial pressure appears to be volume dependent. This result is in agreement with the classic concept of the renin–angiotensin system as a circulating hormonal system involved in the regulation of arterial pressure during hypovolaemia.[3 4 7] In the valsartan group, the overall decrease in MAP is about 30%, which is in the same range as in the placebo group, but without an increase in SVR. Conversely, the 'paradoxical' vasodilatation at 20% BV is still observed at 40% BV. Moreover, the decrease in CI and SV is moderate, observed mainly at 40% BV and is lower than in the placebo group. These effects on VR and CO were not observed in the enalaprilat group. The discrepancy between the two treatments on the determinants of arterial pressure reveals the importance of the specific angiotensin II receptors in mediating the effects of activation of the renin–angiotensin system. Besides the vasodilatory effect, AT_2 stimulation may have some beneficial effect on myocardial function. AT_1 blockade may have a positive effect on left ventricular filling when preload is low, by enhancing left ventricular diastolic function.[6]

Our experimental model has enabled us to demonstrate the different effects of ACE inhibitors and AT_1 antagonists on arterial pressure regulation, and their effects on haemodynamic variables during anaesthesia and haemorrhage. However, short-term treatment and experiments in healthy young pigs cannot be extrapolated to long-term treatment in patients with cardiovascular disease. Nevertheless, the results suggest that further clinical studies that examine the consequences of the two treatments are warranted. The current recommendations for the use of vasoconstrictors in any case of hypotension following anaesthesia in patients treated with renin–angiotensin system antagonists, no matter what kind of renin—angiotensin system antagonist it is, may thus be too simplistic.[13 24]

In summary, the inhibition of the renin–angiotensin system by either the non-specific blockade of the two receptor subtypes, AT_1 and AT_2, with enalaprilat or by the specific blockade of AT_1 with valsartan leads to two different haemodynamic profiles in response to hypovolaemia in the anaesthetized pig. The difference between the two forms of antagonism makes apparent the functions of the AT_2 receptor. Further clinical studies are required to assess the clinical relevance of our findings to patients receiving long-term treatment for various indications.[9–11 25]

Acknowledgements

The authors are grateful to Dr de Gasparo for helpful criticism and to Novartis Laboratories for generously providing valsartan, and Dr Scemama and Merck Sharp Dohme Chibret Laboratories for generously providing enalaprilat

References

1 Breckenridge A. Angiotensin converting enzyme inhibitors. *Br Med J* 1988; **396**: 618–20.

2 Goodfriend TL, Elliott ME, Catt KJ. Angiotensin receptors and their antagonists *N Engl J Med* 1996; **334**: 1649–54

3 Kiowski W, Linder L, Kleinbloesem C, Kleinbloesem C, van Brummelen P, Buhler FR. Blood pressure control by the renin-angiotensin system in normotensive subjects. *Circulation* 1992; **85**: 1–8

4 Sancho J, Re R, Burton J, Barger AC, Haber E. The role of the renin-angiotensin-aldosterone system in cardiovascular homeostasis in normal human subjects *Circulation* 1976; **53**: 400–5

5 Haber E. The role of renin in normal and pathological cardiovascular homeostasis. *Circulation* 1976; **54**: 849–61

6 de Gasparo M, Catt KJ, Inagami T, Wright JW, Unger T. International Union of Pharmacology. XXIII. The angiotensin II receptors. *Pharmacol Rev* 2000; **52**: 415–72

7 Colson P, Ryckwaert F, Coriat P. Renin angiotensin system antagonists and anesthesia. *Anesth Analg* 1999; **89**: 1143–55

8 Carp H, Vadhera R, Jayaram A, Garvey D Endogenous vasopressin and renin-angiotensin systems support blood pressure after epidural block in humans. *Anesthesiology* 1994; **80**: 1000–7

9 Coriat P, Richer C, Douraki T, *et al.* Influence of chronic angiotensin-converting enzyme inhibition on anesthetic induction. *Anesthesiology* 1994; **81**: 299–307

10 Colson P, Saussine M, Séguin JR, Cuchet D, Chaptal PA, Roquefeuil B. Hemodynamic effects of anesthesia in patients chronically treated with angiotensin-converting enzyme inhibitors. *Anesth Analg* 1992; **74**: 805–8

11 Brabant S, Bertrand M, Eyraud D, Darmon PL, Coriat P. The hemodynamic effects of anesthetic induction in vascular surgical patients chronically treated with angiotensin II receptor antagonists. *Anesth Analg* 1999; **88**. 1388–92

12 Matsubara H. Pathophysiological role of angiotensin II type 2 receptor in cardiovascular and renal diseases. *Circ Res* 1998; **83**: 1182–91

13 Eyraud D, Brabant S, Dieudonne N, *et al* Treatment of intraoperative refractory hypotension with terlipressin in patients chronically treated with an antagonist of the renin-angiotensin system. *Anesth Analg* 1999; **88**. 980–4

14 Schadt JC, Ludbrook J. Hemodynamic and neurohumoral responses to acute hypovolemia in conscious mammals. *Am J Physiol* 1991; **260**. H305–18

15 Courneya CA, Korner PI. Neurohumoral mechanisms and the role of arterial baroreceptors in the reno-vascular response to haemorrhage in rabbits. *J Physiol* 1991; **437**: 393–407

16 Cox Rh, Bagshaw RJ. Effects of anesthesia on carotid sinus reflex control of arterial hemodynamics in the dogs. *Am J Physiol* 1980; **239**: H681–91

17 Oliver JR, Korner PI, Woods RL, Zhu JL. Reflex release of vasopressin and renin in hemorrhage is enhanced by autonomic blockade. *Am J Physiol* 1990, **258**: H221–8

18 Korner PI, Oliver JR, Zhu JL, Woods RL. Autonomic, hormonal, and local circulatory effects of hemorrhage in conscious rabbits. *Am J Physiol* 1990, **258**: H229–39

19 Chung O, Kuhl H, Stoll M, Unger T. Physiological and pharmacological implications of AT1 versus AT2 receptors. *Kidney Int Suppl* 1998; **67**: S95–9

20 Scheuer DA, Perrone MH. Angiotensin type 2 receptors mediate depressor phase of biphasic pressure response to angiotensin. *Am J Physiol* 1993; **264**: R917–23

21 Ichiki T, Labosky PA, Shiota C, *et al.* Effects on blood pressure and explanatory behaviour of mice lacking angiotensin II type-2 receptor. *Nature* 1995; **377**: 748–50

22 Siragy HM. The role of AT2 receptor in hypertension. *Am J Hypertens* 2000; **13**: 62S–67S

23 Bindschedler M, Degen P, Flesch G, de Gasparo M. Pharmacokinetic and pharmacodynamic interaction of single oral doses of valsartan and furosemide. *Eur J Clin Pharmacol* 1997; **52**: 371–8

24 Bertrand M, Godet G, Meerschaert K, Brun L, Salcedo E, Coriat P. Should the angiotensin II antagonists be discontinued before surgery? *Anesth Analg* 2001; **92**: 26–30

25 Ryckwaert F, Colson P. Hemodynamic effects of anesthesia in patients with ischemic heart failure chronically treated with angiotensin-converting enzyme inhibitors. *Anesth Analg* 1997; **84**: 945–9

British Journal of Anaesthesia 89 (4): 605–13 (2002)

Apparent diffusion coefficient mapping predicts mortality and outcome in rats with intracerebral haemodynamic disturbance: potential role of intraoperative diffusion and perfusion weighted magnetic resonance imaging to detect cerebral ischaemia

S. Ishikawa[1]*, K. Yokoyama[1], T. Kuroiwa[2] and K. Makita[1]

[1]Department of Anesthesiology and Critical Care Medicine and [2]Department of Neuropathology, Medical Research Institute, Tokyo Medical and Dental University, School of Medicine, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan

**Corresponding author*

Background. Usefulness and ability of diffusion and perfusion weighted magnetic resonance images (DWI and PWI) to detect intracerebral haemodynamic disturbance have not been fully evaluated.

Methods. After the right common carotid artery had been ligated, rats were exsanguinated to maintain a mean arterial pressure of 35, 42, or 50 mm Hg (n=6, each group). Apparent diffusion coefficient (ADC) maps were calculated from DWIs and lesion volume (area) was defined based on ADC values (ADC lesion volume (area)).

Results. ADC lesion volume during exsanguination in the 35 mm Hg group (417 (111) mm^3, P<0.01) was significantly larger than in the 42 mm Hg group (87 (84) mm^3) and 50 mm Hg group (42 (58) mm^3). The low relative cerebral blood flow area, calculated from PWI, was significantly larger during exsanguination in the 35 mm Hg group than in the other groups. ADC lesion volume in the six rats that died within 3 days of the MRI study was significantly larger (median 421 mm^3, range 205–476 mm^3, P<0.005) than in the 12 rats that survived for 3 days (median 26 mm^3, range 3–517 mm^3). Rats with an ADC lesion area over 14 mm^2 on the coronal slice including the caudate putamen during exsanguination died within 3 days or revealed a more severe histopathological outcome than those that survived for 3 days.

Conclusions. Incomplete cerebral ischaemia created by the combination of common carotid artery occlusion and exsanguination could be detected by DWI and PWI both qualitatively and quantitatively. The size of the lesion on ADC mapping was found to correlate with mortality and outcome.

Br J Anaesth 2002; **89**: 605–13

Keywords: brain, ischaemia; measurement techniques, diffusion-weighted magnetic resonance image; measurement techniques, perfusion-weighted magnetic resonance image; rats

Accepted for publication: May 14, 2002

Severe internal carotid artery (ICA) stenosis or occlusion is an important cause of stroke[1] and may be associated with various degrees of haemodynamic impairment.[2 3] Recent research[4] has demonstrated that carotid artery disease is a significant predictor of postoperative stroke after coronary artery bypass surgery. One can postulate that perioperative ischaemic stroke in patients with ICA stenosis or occlusion may be, in part, explained by cerebral hypoperfusion. This cerebral hypoperfusion is most likely the result of systemic hypotension, either as a result of massive haemorrhage or to the effect of drugs administered during the procedure. The effects of perioperative systemic haemodynamic impairment on cerebral perfusion and the outcome of such patients have not yet been fully investigated. However, new technological advances are making these investigations possible.

Diffusion and perfusion weighted imaging (DWI and PWI) are two relatively new modalities of magnetic

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

resonance imaging (MRI). DWI has been well established as a reliable non-invasive method for the early detection of cerebral ischaemic stroke.[5 6] Even before lesions become apparent on conventional images, DWI can detect abnormalities within minutes after the onset of ischaemia in animal models of stroke.[7–9] With DWI, the signal intensity in ischaemic brain regions appears high because the diffusion coefficient of water is reduced, likely because of the formation of cytotoxic oedema.[10 11] This can be quantified by the calculation of apparent diffusion coefficient (ADC) images.[12 13] PWI uses gradient echo imaging to follow a fast bolus injection of magnetically susceptible contrast agent. Following ischaemia, perfusion deficits can be observed as decreases in contrast bolus transit.

Three hypotheses formed the basis of the present study. First, it was postulated that intracerebral haemodynamic disturbance can be detected by DWI and PWI, not only qualitatively but also quantitatively. To date, DWI and PWI have been used in experimental animal studies using the middle cerebral artery occlusion model.[14] There have been few investigations that use DWI and PWI to document the changes that occur with incomplete cerebral ischaemia. Secondly, if these MRI modalities can detect the spatial evolution of cerebral ischaemic lesions, then perhaps a relationship between lesion volume and mortality could be established. As yet, despite the high mortality rate of perioperative stroke,[15] there are no reliable indicators which can predict mortality as a result of cerebral ischaemia. Finally, DWI should be able to predict the severity of cerebral ischaemic injury. In experimental studies, the extent of cerebral ischaemic injury is evaluated histopathologically by examination of specific brain slices. Thus, if the cerebral ischaemia detected by DWI reflects the severity of cerebral injury, a relationship between the ischaemic lesion seen on DWI and histopathologic diagnosis may exist.

Methods

This project was approved by, and followed the guidelines published by, the Animal Care and Use Committee of Tokyo Medical and Dental University.

Animal preparation

Eighteen adult male Sprague–Dawley rats weighing between 330 and 400 g were used. Anaesthesia was induced with 4% isoflurane in a Plexiglas chamber. The concentration of isoflurane was then reduced to 1.5%, and 1% lidocaine was injected locally for analgesia. Under an operating microscope, the bifurcation of the right common carotid artery was exposed through a midline neck incision and was ligated in duplicate with 3-0 silk surgical thread. A polyethylene catheter (PE-50) was introduced into the right femoral vein for drug infusion. Physiologic saline solution at 4 ml kg^{-1} h^{-1} was administered i.v. throughout the study. Two PE-50 catheters were introduced into femoral arteries on both sides. One arterial catheter was used for continuous arterial pressure monitoring and the other was used for blood withdrawal and arterial blood sampling. After tracheal intubation, each rat was ventilated with 40% oxygen and the ventilatory frequency was controlled to maintain a Pa_{CO_2} of approximately 40 mm Hg except during exsanguination. The ventilatory frequency was not changed during exsanguination, and a relative hypocapnoea was allowed to develop because frequent arterial blood sampling, which is necessary to maintain normocapnea, would have made it difficult to maintain the pre-set mean arterial pressure.

Experimental procedure

After placing the animals supine in the probe, anaesthesia was maintained with 1.5% isoflurane in 40% oxygen. The rat's body temperature was monitored with a rectal probe, and maintained at 37.5 (0.5)°C using a water-circulating heating pad during the MRI study. Details of the MRI study and the data analysis are given in the Appendix. After animal positioning and shimming, a set of baseline DWIs was acquired.

The animals were randomly allocated to three groups according to mean arterial pressure (MAP) (35, 42, and 50 mm Hg groups, n=6 each) maintained for 30 min by blood withdrawal. Arterial blood was withdrawn through one of the femoral arterial catheters to the pre-set MAP to induce intracerebral haemodynamic disturbance. Fluctuation of ±1 mm Hg from the target arterial pressure was allowed. DWIs were commenced at 10 min after the MAP reached the pre-set value. After 30 min of the ischaemic period, a paramagnetic nuclear magnetic resonance contrast agent (0.5 mmol kg^{-1} gadolinium diethylenetriamine pentaacetic acid; Magnevist, Berlex, USA) was rapidly injected into the right femoral vein. Acquisition of PWIs began approximately 20 s before contrast injection and continued for a total of 80 images. After the completion of PWIs, the withdrawn blood was re-administered i.v. for approximately 10 min. Post-ischaemic DWIs were acquired at 0 and 30 min after completion of the administration of the withdrawn blood.

After extubation, the animals were kept in an oxygen-rich chamber. Their rectal temperature was maintained at 37.5 (0.5)°C using a water-circulating pad for 3 h. They were then released into their home cage.

Arterial blood samples were collected at baseline and 10 min after the completion of the re-infusion of the withdrawn blood. Other arterial blood samples were collected as needed. Samples were analysed on a laboratory blood gas analyzer (STAT profile 5™ gas analyzer, NOVA Biomedical, USA). Metabolic acidosis was treated by the i.v. administration of sodium bicarbonate.

Definition of lesion area (volume) and low perfusion area

The ischaemic lesion area and the low perfusion area were defined arbitrarily as the pixels in which the ADC, relative cerebral blood volume (rCBV), and relative cerebral blood flow (rCBF) value decreased to less than a predetermined threshold on each map. Calculation of ADC, rCBV, and rCBF are given in the Appendix. The threshold was set at 500×10^{-6} mm^2 s^{-1} on ADC map,[16 17] 50% of the mean rCBV and rCBF of the left (contralateral) hemisphere on rCBV map and rCBF map, respectively. The lesion area on the ADC map and the low perfusion area on the rCBV and the rCBF map (ADC lesion area, low rCBV area, and low rCBF area, respectively) were calculated by multiplying the number of these pixels by the area of one pixel. Lesion volume of ischaemic injury was determined by integration of the ADC lesion areas for the nine slices (ADC lesion volume).

Histopathology

Neurohistopathology was rated in those rats that survived for 3 days following the MRI study. After each rat was anaesthetized with isoflurane, the chest was opened, and the brain was perfused by transcardial perfusion with 20 ml of isotonic saline followed by 20 ml of 10% buffered formalin. The brain was then removed and stored in 10% formalin for 1 week. The brain was cut into coronal blocks and embedded in paraffin, and 6-µm sections were sliced and mounted on slides. The slides were stained with hematoxylin and eosin and examined using light microscopy. The examiner was blinded to the results of the MRI study. Neuronal histopathology was evaluated in the coronal section at the level of the caudate nucleus (8.6–9.7 mm anterior to the interaural line[18]). The ischaemic damage of this section had been evaluated by ADC map, rCBV map, and rCBF map. Neuronal damage was graded on a five-point scale with the following markers:[19] 0=no observable neuronal death; 1=scattered neuronal death; 2=small focal damage in caudate and cortical areas; 3=large infarcts involving 50% of ischaemic hemisphere; and 4=total hemisphere infarct.

Statistical analysis

MAP, arterial blood gas data, blood glucose concentration, rectal temperature, and ADC lesion volumes were analysed using two-way repeated measures analysis of variance followed by the Tukey multiple comparison test. Baseline, 10 min after MAP reached the pre-set value, and 10 min after the completion of blood reinfusion, MAP and rectal temperatures were compared. Low rCBV area and low rCBF area were compared among the groups using one-way analysis of variance followed by the Tukey multiple comparison test. The relationships between ADC lesion area and low rCBV area and between ADC lesion area and low rCBF area on the slice including the caudate putamen were analysed using linear fitting. ADC lesion volume was compared between surviving and dead animals using the Mann–Whitney *U* test because D'Agostino-Pearson test revealed that the spread and skew of data made parametric statistics inappropriate. Statistical significance was established at the *P*<0.05 level.

Table 1 MAP, arterial blood gas, blood glucose concentration, and rectal temperature in three groups. Data are mean (SD). Glc=blood glucose concentration. $^{*}P<0.05$, $^{**}P<0.01$ *vs* baseline. $^{\#}P<0.05$, $^{\#\#}P<0.01$ *vs* 42 mm Hg group. $^{+}P<0.05$, $^{++}P<0.01$ *vs* 50 mm Hg group

		Baseline	**Exsanguination**	**Re-infusion**
MAP	35 mm Hg	113 (6)	35 (1)$^{**\#\#++}$	96 (12)$^{**\#++}$
(mm Hg)	42 mm Hg	111 (13)	42 (1)$^{**++}$	124 (13)
	50 mm Hg	101 (8)	50 (1)**	136 (18)**
pH	35 mm Hg	7.41 (0.02)		7.07 (0.07)$^{**\ \#\#++}$
	42 mm Hg	7.39 (0.03)		7.30 (0.05)**
	50 mm Hg	7.38 (0.03)		7.37 (0.05)
Pa_{O_2}	35 mm Hg	176 (16)		200 (22)
(mm Hg)	42 mm Hg	180 (12)		186 (17)
	50 mm Hg	180 (28)		168 (36)
Pa_{CO_2}	35 mm Hg	39.3 (3.6)		38.4 (2.5)
(mm Hg)	42 mm Hg	37.7 (2.3)		38.8 (3.3)
	50 mm Hg	40.0 (3.8)		39.1 (2.2)
BE	35 mm Hg	1.2 (0.8)		−17.7 (2.6)$^{**\ \#\#++}$
(mmol litre^{-1})	42 mm Hg	−1.0 (1.8)		−6.4 (2.4) $^{**+}$
	50 mm Hg	−0.6 (1.6)		−2.0 (2.7)
Glc	35 mm Hg	129 (14)		80 (6)$^{**++}$
(mg dl^{-1})	42 mm Hg	125 (29)		106 (31)$^{+}$
	50 mm Hg	115 (20)		148 (35)
Rectal temperature	35 mm Hg	37.4 (0.3)	37.5 (0.4)	37.4 (0.3)
(°C)	42 mm Hg	37.4 (0.2)	37.5 (0.3)	37.6 (0.3)
	50 mm Hg	37.4 (0.3)	37.4 (0.2)	37.6 (0.3)

Results

The MRI study was performed without any serious complications. The amount of blood volume which was required to be withdrawn until the MAP reached the pre-set value in the 35 mm Hg group (8.4 (0.9) ml, $P<0.01$) was significantly greater than in the 42 mm Hg group (6.5 (0.6) ml) and the 50 mm Hg group (4.5 (0.9) ml). Five rats in the 35 mm Hg group and one rat in the 42 mm Hg group died over the 3-day observation period.

MAP in the 35 mm Hg group was significantly lower than in the 42 mm Hg group ($P<0.05$) and in the 50 mm Hg group ($P<0.01$) at 10 min after the completion of the blood reinfusion (Table 1). Both arterial pH and base excess (BE) were also significantly lower in the 35 mm Hg group than in the other two groups during the reinfusion period ($P<0.01$). Blood glucose concentration in the 35 mm Hg group was lower than in the 50 mm Hg group ($P<0.01$) at re-infusion, but no significant difference was found between the 35 mm Hg and 42 mm Hg groups. Twelve rats (6, 5, and 1 rats in the 35, 42, and 50 mm Hg groups, respectively) needed i.v. sodium bicarbonate. Their arterial pH and BE were confirmed to be within normal limits at the end of the MRI study (pH 7.40 (0.05), BE −1.4 (1.7)).

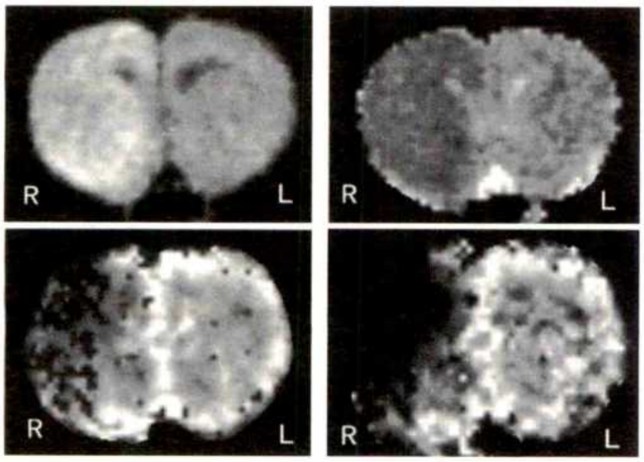


Fig 1 Diffusion-weighted image (upper left) and ADC map (upper right) during exsanguination, rCBV map (lower left), and rCBF map (lower right) of a representative rat in the 35 mm Hg group.

At baseline, neither DWIs nor ADC maps documented any abnormal regions in any of the rats. Representative DWI, ADC map, rCBV map, and rCBF map during exsanguination in the 35 mm Hg group are shown in Figure 1. These representative data indicate that: DWI revealed increased signal intensity in most regions of the right hemisphere; a clear reduction in the ADC value was evident in these regions; the low intensity region on the ADC map corresponded well with that of the rCBF map; however, the rCBV map showed a smaller region with a low rCBV value (Fig. 1).

There was no significant difference in ADC lesion volume among the groups at baseline. In the ipsilateral hemisphere, ADC lesion volumes during exsanguination in the 35 mm Hg group and in the 42 mm Hg group (417 (111) and 87 (84) mm^3, respectively) were significantly larger than at baseline ($P<0.01$ and $P<0.05$, respectively) (Fig. 2). There was no significant difference in ADC lesion volumes

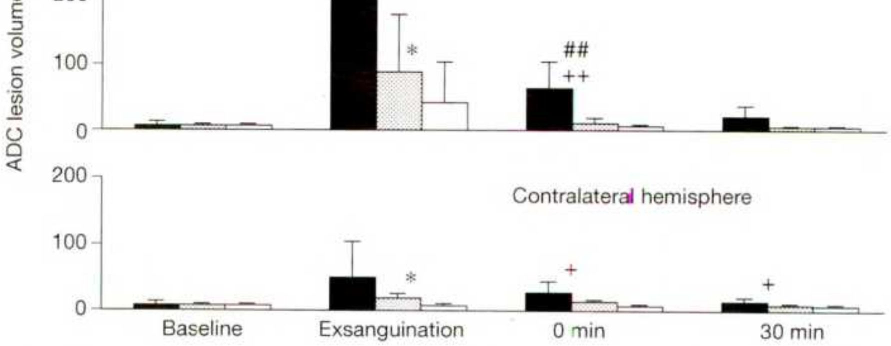


Fig 2 Sequential changes in ADC lesion volume in the ipsilateral (upper) and contralateral hemisphere (lower) of the 35 (black), 42 (grey), and 50 mm Hg (white) groups. Data are expressed as mean (SD). 0 min, 30 min represent 0 and 30 min after the completion of the infusion of the withdrawn blood, respectively. $^{*}P<0.05$, $^{**}P<0.01$ *vs* baseline. $^{\#\#}P<0.01$ *vs* 42 mm Hg group. $^{+}P<0.05$, $^{++}P<0.01$ *vs* 50 mm Hg group.

in the 50 mm Hg group at different time points. ADC lesion volumes in the 35 mm Hg group during exsanguination and at 0 min after the completion of blood re-infusion were significantly larger than in the 42 and 50 mm Hg groups ($P<0.01$), but there was no significant difference between the 42 and 50 mm Hg groups at any time point. After blood re-infusion, ADC lesion volume decreased in all groups and there was no significant difference compared with baseline. Smaller sequential changes in ADC lesion volumes were observed in the contralateral hemisphere (Fig. 2).

Low rCBV area in the 35 mm Hg group (21.2 (17.2) mm^2) was significantly larger than in the 50 mm Hg group (5.5 (2.3) mm^2, $P<0.05$) (Fig. 3). There was no significant difference between the 35 and 42 mm Hg groups (6.4 (4.0) mm^2). Low rCBF area in the 35 mm Hg group (26.2 (15.9) mm^2) was significantly larger than in the 42 mm Hg group (6.9 (5.5) mm^2, $P<0.05$) and the 50 mm Hg group (4.0 (1.8) mm^2, $P<0.01$). Linear regression analyses demonstrated that there were significant linear relationships between ADC lesion area and low rCBV area ($r=0.73$, $P<0.01$) and also between ADC lesion area and low rCBF area ($r=0.85$, $P<0.01$) on the slice including the caudate putamen (Fig. 4).

Of note, the ADC lesion volume during exsanguination was significantly larger in the six rats (median 421 mm^3 (range 205–476 mm^3), $P<0.005$) that died within 3 days than in the 12 rats that survived (median 26 mm^3 (range 3–517 mm^3)). In addition, there was a significant difference in the ADC lesion volume 30 min after re-infusion of the withdrawn blood between the animals that died within 3 days (median 17 mm^3 (range 2–53 mm^3), $P<0.05$) and the animals that survived (median 4 mm^3 (range 2–11 mm^3)) (Fig. 5).

Histopathological analysis was performed in the 12 rats that survived for 3 days following the MRI study. Of the 12 animals, two animals had a neuronal damage score of 0 (one from the 42 mm Hg group and one from the 50 mm Hg group), eight had a neuronal damage score of 1 (four from the 42 mm Hg group and four from the 50 mm Hg group), and two had a neuronal damage score of 2 (one from the 35 mm Hg group and one from the 50 mm Hg group). No animals had a neuronal damage score of 3 or 4. The histopathology of the rats with a score of 1 or 2 demonstrated neuronal death (Fig. 6) predominantly in the border zone area.

Figure 7 shows the relationship between the ADC lesion area of the specific coronal slice including the caudate putamen and the neuronal damage score. The ADC lesion areas clearly showed a two-part distribution depending on the score. ADC lesion areas of the animals that died or showed a neuronal damage score of 2 were more than 14 mm^2. In those animals whose neuronal damage score was 0 or 1, the ADC lesion areas were less than 11 mm^2. Moreover, in those animals that survived, the ADC map at 30 min after the completion of the blood re-infusion displayed a very small lesion area (less than 0.6 mm^2) on the slice including the caudate putamen.

Discussion

We ligated the right common carotid artery in rats and induced an intracerebral haemodynamic disturbance by exsanguination. The resulting incomplete cerebral ischaemia was successfully imaged using DWI and PWI. Lesion volume based on DWI and low perfusion area calculated from PWI significantly increased as the exsanguination evolved. ADC maps demonstrated larger ischaemic lesion volumes in the animals that died within 3 days than in those that survived. A larger ADC lesion area correlated well with

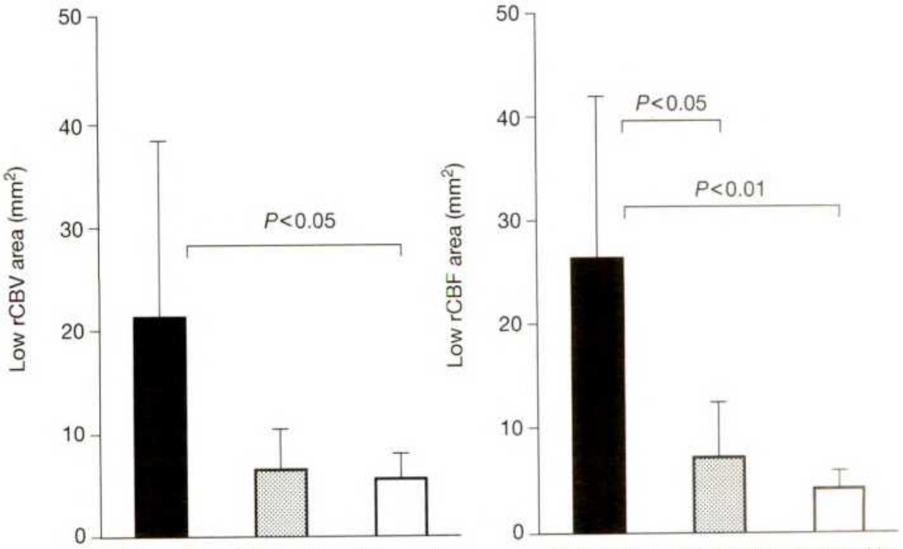


Fig 3 Low rCBV area (left) and low rCBF area (right) in the 35 (black), 42 (gray), and 50 mm Hg (white) groups. Data are expressed as mean (SD).

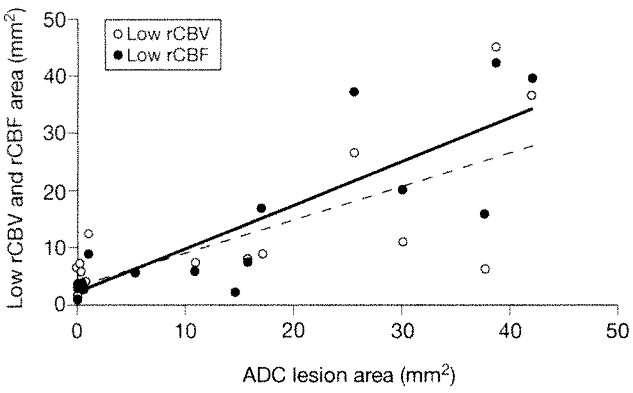


Fig 4 Relationships between ADC lesion area during exsanguination and low rCBV area and between ADC lesion area and low rCBF area on the coronal slice including the caudate putamen. There was a significant linear relationships between ADC lesion area and low rCBV area ($y=0.58x+3.3$ ($r=0.73$, $P<0.01$), dashed line) and ADC lesion area and low rCBF area ($y=0.77x+2.2$ ($r=0.85$, $P<0.01$), thick line).

a more severe outcome (death or worse neuronal damage score).

By combining DWI and PWI in this study, we were able to show that there were significant linear relationships between the ADC lesion area and low rCBF area, and between ADC lesion area and low rCBV area on the slice including the caudate putamen. The first relationship suggests that these ischaemic lesions caused by low cerebral perfusion enlarged as the exsanguination evolved. Furthermore, our findings suggest that ADC mapping could be used not only to detect intracerebral haemodynamic disturbances qualitatively, but also to quantify them. In fact, with the ADC lesion volume (area) defined using a predetermined threshold,[16 17] the spatial evolution of the cerebral ischaemic injury was clearly demonstrated as the exsanguination evolved. The linear relationship between the ADC lesion area and low rCBV area suggests that cerebral vasodilation had become maximal and that the vessel had already begun collapsing when the ischaemic lesion was detected on the ADC map. The different behaviour against cerebral perfusion pressure (CPP) between rCBV and rCBF[2 20] may partially explain smaller low rCBV area than low rCBF area in the representative rat (Fig. 1).

In our study, we varied target arterial pressure (35, 42, or 50 mm Hg) to create various degrees of cerebral ischaemic injury. As expected, lesion volume based on the ADC map showed wide variation among the animals. When we compared the results of those animals that died within 3 days with those that survived, there was a significant difference in ADC lesion volume, with surviving animals having smaller lesions. It would appear that ADC lesion volume reflects the spatial evolution of cerebral ischaemia and thus correlates with the severity of the cerebral injury. Large lesions may have been the crucial factor that resulted in the death of the animals.

ADC lesion volume after blood re-infusion was also compared between those animals that died within 3 days and those that survived. Regions with low ADC values after reperfusion are likely to infarct, because they reflect tissues with irreversible ischaemic damage. This has been documented in the transient middle cerebral artery occlusion model.[7–9] In 10 of the 12 animals that survived, the histopathological analyses demonstrated neuronal damage but not pannecrosis. The fact that these animals also showed very small ADC lesions area (less than 0.6 mm²) on the slice including the caudate putamen at 30 min after blood re-infusion supports the assumption that the cerebral ischaemia was not severe in such animals. The cerebral injury was mostly reversible, although damaged neurones were seen predominantly in the border zone area. When ADC lesion areas on the specific coronal slice were compared to the neuronal damage scores, there seemed to be a threshold of ADC lesion area (14 mm²) over which a more severe outcome (death or neuronal damage score 2) was likely. The relationship between the ADC lesion area and the neuronal damage score observed in the present study suggests that ADC mapping may be useful in predicting histopathological outcome in animals that survive intracerebral haemodynamic disturbance.

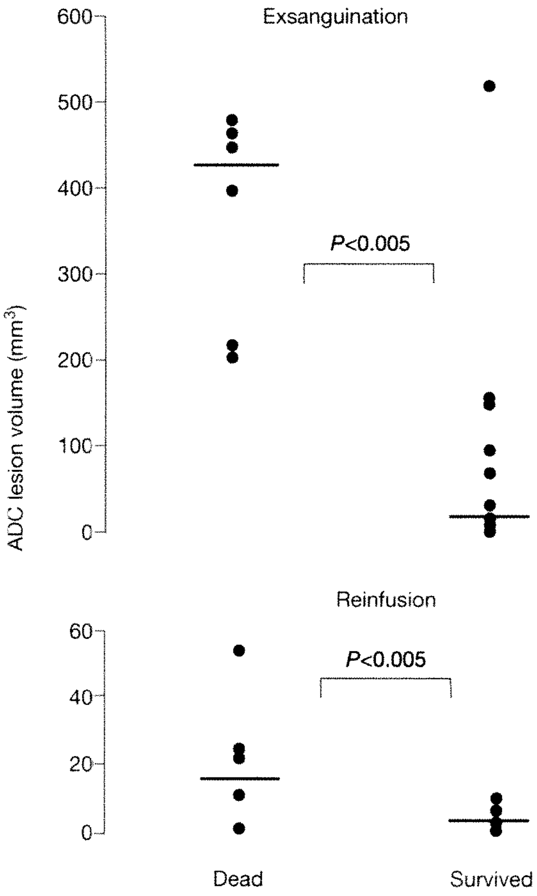


Fig 5 ADC lesion volume during exsanguination (upper) and after re-infusion of blood (lower) in dead and survived rats. ADC lesion volumes in dead animals were significantly larger than those animals who survived in both periods. Horizontal lines indicate median values.

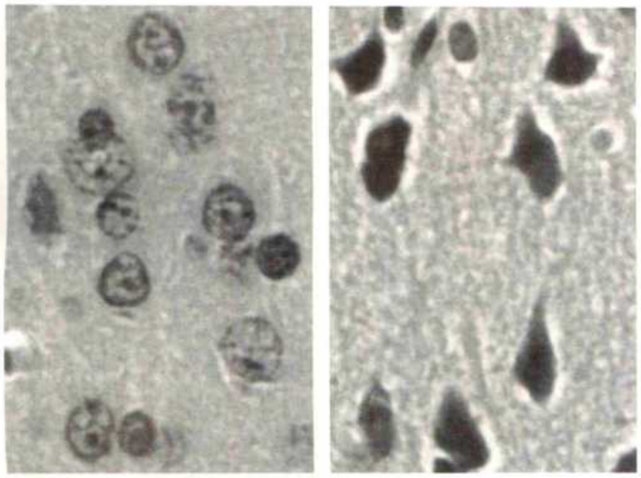


Fig 6 Histopathologic findings of the ipsilateral cortex in experimental rats 3 days after the MRI study (hematoxylin & eosin, original magnification ×400). (Left) Intact neurones, (right) dark neurones. Dark neurones were seen in the rats with a neuronal damage score of 1 or 2 predominantly in the border zone area.

It was also observed that a significantly lower MAP in the 35 mm Hg group occurred after re-infusion of the withdrawn blood (Table 1). This may in part be explained by the occurrence of a more severe metabolic acidosis in this group. However, as the acid–base abnormality returned to near normal at the end of the MRI study, the effect of transient metabolic acidosis on outcome may be small. It was also noted that a difference in blood glucose concentration occurred among the groups following the blood re-infusion (Table 1). This may be explained by the fact that significantly more blood was withdrawn in the 35 mm Hg group. Blood glucose may have been partly glycolysed by erythrocytes[21] and the re-infused blood may have diluted the existing blood glucose of the rats in the 35 mm Hg group. However, as the outcome of the animals in the 35 mm Hg group was the worst despite the lower blood glucose concentration, the impact on outcome of the difference in blood glucose concentration may not be substantial.

Presently, MRI systems are being developed both for clinical use and for intraoperative use during neurosurgical procedures performed under general anaesthesia.[22–24] Already, DWI can be performed to determine whether cerebral ischaemia or infarction has occurred following completion of the procedure before the patient leaves the operating room.[25] The results of the present study suggest that intraoperative DWI and PWI could potentially be used to detect early abnormalities of intracerebral haemodynamics and thus alert the surgeon to the occurrence of cerebral ischaemia as a result of compromised CBF. This would facilitate the introduction of brain protective measures, such as hypothermia. In addition, intraoperative MRI could potentially become a decision-making tool for the neurosurgeon. For example, the decision as to whether or not to insert a shunt during carotid endarterectomy could depend on the results of intraoperative MRI.

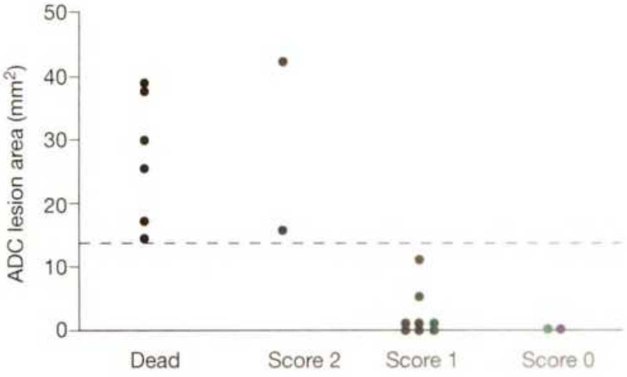


Fig 7 ADC lesion area during exsanguination of dead animals and rats with neuronal damage score 0, 1, and 2. ADC lesion areas of the animals which were dead or showed neuronal damage score 2 was more than 14 mm^2 (dashed line) but those of the rats whose neuronal damage score was 0 or 1 were less than 11 mm^2.

However, intraoperative DWI and PWI techniques as they stand are not yet ready for clinical detection of intraoperative cerebral ischaemia or prediction of mortality and outcome in patients. The development process towards clinical application will require several problems to be overcome. First, the cost of the complete system of intraoperative MRI must be markedly reduced before widespread use becomes possible. MRI-compatible surgical instruments including titanium forceps, titanium scissors, and titanium retractors are required, and anaesthesia machines and monitors should also be MRI compatible. Secondly, the size of the MRI scanner must be reduced to allow surgeons to obtain optimal access to patients. However, this should not be achieved at the expense of homogeneity of the magnetic field or function of the MRI system. Lastly, the abilities of DWI and PWI to detect incomplete cerebral ischaemia and to predict mortality and outcome must be validated in humans.

In conclusion, DWI and PWI both qualitatively and quantitatively delineated intracerebral haemodynamic disturbances. They clearly demonstrate the spatial evolution of the cerebral ischaemic injury as the exsanguination evolved. During incomplete cerebral ischaemia, the measurement of lesion volume as detected by ADC mapping predicted mortality. Larger ischaemic lesions detected by ADC map on the coronal section, which included the caudate putamen were associated with a more severe outcome (death or small focal damage). In the future, intraoperative DWI and PWI have the potential to facilitate the early detection of intracerebral haemodynamic disturbances, thus allowing a timely and effective response.

Acknowledgement

This study was partly supported by a Grant-in-Aid (A) (No. 12770810) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Appendix

MR imaging and data analysis

MRI

MRI was performed using a 4.7-T experimental imager/spectrometer system (Unity INOVA, Varian, Palo Alto, CA, USA) with a 330-mm horizontal bore magnet equipped with shielded gradients (maximal strength, 65 mT m^{-1}) and an 80-mm-ID quadrature detection coil. The slice plane was standardized by first obtaining preview spin-echo images.

DWI

Spin-echo DWIs (TR ms/TE ms=2000/64, 40-mm field of view, 128×128 matrix, 2-mm section thickness) consisted of nine coronal slices covering most of the rat brain. Diffusion weighting was applied along all three axes (b=0 and 1100 s mm^{-2}). A single DWI required an acquisition time of approximately 18 min. DWI with a b value of 0 s mm^{-2} corresponds to a T2-weighted image.

PWI

PWIs were acquired using a gradient echo imaging sequence (TR ms/TE ms=14/8, 10° flip angle, 40-mm field of view, 64×64 matrix, 2-mm section thickness, 1 image s^{-1}) to follow a fast bolus injection of magnetic susceptibility contrast agent. The single PWI slice was chosen to coincide with one of the DWI slices and the histopathology examination.

MRI data analysis

Pairs of DWIs with two b values were used to generate maps of the ADC. ADC maps were calculated using the standard equation:[26]

$$ADC = \ln (S_0/S_1)/(b_1 - b_0)$$

where S_0 and S_1 are the signals of the two DWI scans and b_0 and b_1 are 0 and 1100 s mm^{-2}.

Signal intensity of PWIs was converted to the change in the T_2 rate, $\Delta R_2^*(t)$, using the standard equation:[27 28]

$$\Delta R_2^*(t) = \ln [S(t)/S(0)]/TE$$

where $S(t)$ is the signal intensity at time t during passage of the contrast agent, $S(0)$ is the baseline value of the pre-contrast signal intensity, and TE is echo time. As $\Delta R_2^*(t)$ is proportional to the contrast agent concentration–time curves, it can be used to estimate perfusion parameters.

Assessment of rCBV can be calculated by integrating the $\Delta R_2^*(t)$ time curve with respect to time. The behaviour of the physiological time series data as a contrast agent passes through the vascular bed is closely represented by the gamma-variate curve.[29] To generate rCBV data without the effects of contrast recirculation, the area under the fitted gamma-variate curve was integrated.

An estimate of the vascular transit time (VTT) was obtained by subtracting the time of arrival of the contrast agent in the cerebral tissue from the first moment of the fitted gamma-variate curve. The estimates of VTT and rCBV were used to calculate the rCBF by using the equation of the central volume principle:[30]

$$rCBF = rCBV/VTT$$

where rCBF was determined for each pixel.

References

1 Barnett JJM, Mohr JP, Stein BM, Yatsu FM. *Stroke: Pathophysiology, Diagnosis and Management*, 2nd Edn. New York, NY: Churchill-Livingstone, 1992

2 Powers WJ. Cerebral hemodynamics in ischemic cerebrovascular disease. *Ann Neurol* 1991; **29**: 231–240

3 Derdeyn CP, Grubb RL Jr, Powers WJ. Cerebral hemodynamic impairment: methods of measurement and association with stroke risk. *Neurology* 1999; **53**: 251–259

4 Stamou SC, Hill PC, Dangas G, *et al.* Stroke after coronary artery bypass: incidence, predictors, and clinical outcome. *Stroke* 2001; **32**: 1508–1513

5 Rordorf G, Koroshetz WJ, Copen WA, *et al.* Regional ischemia and ischemic injury in patients with acute middle cerebral artery stroke as defined by early diffusion-weighted and perfusion-weighted MRI. *Stroke* 1998; **29**: 939–943

6 van Everdingen KJ, van der Grond J, Kappelle LJ, Ramos LMP, Mali WPTM. Diffusion-weighted magnetic resonance imaging in acute stroke. *Stroke* 1998; **29**: 1783–1790

7 Minematsu K, Fisher M, Li L, *et al.* Effects of a novel NMDA antagonist on experimental stroke rapidly and quantitatively assessed by diffusion-weighted MRI. *Neurology* 1993; **43**: 397–403

8 Minematsu K, Fisher M, Li L, Sotak CH. Diffusion and perfusion magnetic resonance imaging studies to evaluate a noncompetitive *N*-methyl-D-aspartate antagonist and reperfusion in experimental stroke in rats. *Stroke* 1993; **24**: 2074–2081

9 Lo EH, Matsumoto K, Pierce AR, Garrido L, Luttinger D. Pharmacologic reversal of acute changes in diffusion-weighted magnetic resonance imaging in focal cerebral ischemia. *J Cereb Blood Flow Metab* 1994; **14**: 597–603

10 Fisher M, Sotak CH, Minematsu K, Li L. New magnetic resonance techniques for evaluating cerebrovascular disease. *Ann Neurol* 1992; **32**: 115–122

11 Benveniste H, Hedlund LW, Johnson A. Mechanism of detection of acute cerebral ischemia in rats by diffusion-weighted magnetic resonance microscopy. *Stroke* 1992; **23**: 746–754

12 Bihan DL, Breton E, Lallemand D, Grenier P, Cabanis E, Laval-Jeantet M. MR imaging of intravoxel incoherent motions: application to diffusion and perfusion in neurologic disorders. *Radiology* 1986; **161**: 401–407

13 Bihan DL, Moonen CTW, van Zijl PCM, Pekar J, DesPres D. Measuring random microscopic motion of water in tissues with MR imaging: a cat brain study. *J Comput Assist Tomogr* 1991; **15**: 19–25

14 Li F, Liu KF, Silva MD, *et al.* Transient and permanent resolution of ischemic lesions on diffusion-weighted imaging after brief periods of focal ischemia in rats: correlation with histopathology. *Stroke* 2000; **31**: 946–954

15 Parikh S, Cohen JR. Perioperative stroke after general surgical procedures. *NY State J Med* 1993; **93**: 162–165

16 Ishikawa S, Yokoyama K, Kuroiwa T, Makita K. Evolution of cerebral ischaemia induced by thromboembolism in rats detected by early sequential MR imaging. *Br J Anaesth* 2001; **87**: 469–476

17 Morikawa S, Inubushi T, Ishii H, Nakasu Y. Effects of blood sugar level on rat transient focal brain ischemia consecutively observed by diffusion-weighted EPI and ^{1}H echo planar spectroscopic imaging. *Magn Reson Med* 1999; **42**: 895–902

18 Paxinos G, Watson C. *The Rat Brain in Stereotaxic Coordinates*, 4th Edn. New York, NY: Academic Press Inc., 1982

19 Hoffman WE, Braucher E, Pelligrino DA, *et al.* Brain lactate and neurologic outcome following incomplete ischemia in fasted, nonfasted, and glucose-loaded rats. *Anesthesiology* 1990; **72**: 1045–1050

20 Sette G, Baron JC, Mazoyer B, Levasseur M, Pappata S, Crouzel C. Local brain haemodynamics and oxygen metabolism in cerebrovascular disease: positron emission tomography. *Brain* 1989; **112**: 931–951

21 Glycolysis and the catabolism of hexoses. In: Lehninger AL, Nelson DL, Cox MM, eds. *Principles of Biochemistry*, 2nd Edn. New York, NY: Worth Publishers, 1993: 400–445

22 Black PMcL, Moriarty T, Alexander E III, *et al.* Development and implementation of intraoperative magnetic resonance imaging and its neurosurgical applications *Neurosurgery* 1997; **41**: 831–845

23 Hall WA, Martin AJ, Liu H, Nussbaum ES, Maxwell RE, Truwit CL Brain biopsy using high-field strength interventional magnetic resonance imaging. *Neurosurgery* 1999; **44**: 807–814

24 Steinmeier R, Fahlbusch R, Ganslandt O, *et al.* Intraoperative magnetic resonance imaging with the Magnetom Open scanner: concepts, neurosurgical indications, and procedures—a preliminary report. *Neurosurgery* 1998; **43**: 739–748

25 Hall WA, Liu H, Martin AJ, Pozza CH, Maxwell RE, Truwit CL. Safety, efficacy, and functionality of high-field strength interventional magnetic resonance imaging for neurosurgery. *Neurosurgery* 2000; **46**: 632–642

26 Le Bihan D, Breton E, Lallemand D, *et al* Separation of diffusion and perfusion in intravoxel incoherent motion MR imaging. *Radiology* 1988; **168**· 497–505

27 Belliveau JW, Rosen BR, Kantor HL, et *al.* Functional imaging by susceptibility-contrast NMR. *Magn Reson Med* 1990, **14**: 538–546

28 Hamberg LM, Macfarlane R, Tasdemiroglu E, *et al.* Measurement of cerebrovascular changes in cats after transient ischemia using dynamic magnetic resonance imaging. *Stroke* 1993; **24**· 444–451

29 Thompson HK, Starmer CF, Whalen RE, McIntosh HD. Indicator transit time considered as a gamma variate. *Circ Res* 1964, **14**. 502–515

30 Meier P, Zierler KL. On the theory of the indicator-dilution method for measurement of blood flow and volume *J Appl Physiol* 1954; **6**. 731–744

British Journal of Anaesthesia 89 (4): 614–21 (2002)

Mechanisms of action of midazolam on expression of contextual fear in rats

L. Pain[1 3]*, A. Launoy[1], N. Fouquet[2] and P. Oberling[2]

[1]GRERCA, Hôpitaux Universitaires de Strasbourg and INSERM U405, Faculté de Médecine, Strasbourg, France. [2]Institut de Physiologie de la Faculté de Médecine and INSERM U405, Faculté de Médecine, Strasbourg, France

[3]Present address: Department of Psychology, University of Vermont, Burlington, VT 05405, USA

**Corresponding author: U405 Inserm, Faculté de Médecine, 11 rue Humann, F-67085 Strasbourg Cedex, France*

Background. Midazolam may suppress conditioned fear after an aversive event by disrupting the memory trace formed during conditioning, by altering the emotional part of the aversive event, or by the combination of both effects. The purpose of the present study was to determine whether affective-related processes contribute to the amnesic-like effects of midazolam on aversive events.

Methods. The effects of acute administration of low doses of midazolam (0.37–3 mg kg^{-1}) on fear conditioning (association between a neutral context and an aversive stimulus) and on innate anxiety in fearful surroundings were examined in rats. The effect of midazolam on the deleterious consequences of pre-exposure to the context (a non-aversive event) for subsequent fear conditioning was then compared with its effect on fear conditioning. The role of midazolam as an affective context was assessed by performing the testing phase under midazolam. Possible locomotor impairment or long-term effects of midazolam were controlled in additional experiments.

Results. Midazolam reduced both contextual fear conditioning and spontaneous fear. The deleterious effect of midazolam on pre-exposure to the context was of the same magnitude as its effect on the acquisition phase of fear conditioning. The effects of midazolam on both pre-exposure to the context and fear conditioning were unchanged when rats received a second injection of midazolam before the retention phase.

Conclusions. Low doses of midazolam that do not impair locomotion suppress conditioned fear to the context by acting on memory processes rather than on affective or anxiolytic processes.

Br J Anaesth 2002; **89**: 614–21

Keywords: hypnotics, benzodiazepine, midazolam; memory; model, rat; psychological responses

Accepted for publication: May 14, 2002

Some forms of learning and memory may be preserved despite the decrease in cortical awareness that results from the use of sedative agents.[1–4] In clinical practice, midazolam is largely used to alleviate anxiety and to prevent memory (implicit or explicit) of frightening experiences in patients. Benzodiazepines are known to impair the recall of information, especially when administered shortly before the occurrence of the event for which information is to be encoded.[3 5–7] However, the mechanism by which benzodiazepines act on the recall of events that have an aversive component remains unclear. Interactions between affective and mnemonic processes of benzodiazepines cannot be excluded when dealing with the recall of aversive events.[8–11] In this respect, midazolam has been shown to display not only amnesic effects[12–15] but also potent affective properties, such as anxiolysis[16] and a pleasant affective state.[17]

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Midazolam might therefore interact with the emotional component of an aversive event because of its affective properties. More data are thus necessary on the mechanisms by which midazolam acts on the learning and memory for aversive events.

During sedation for medical and/or surgical procedures, the patient experiences passively aversive information that needs to be discarded. This clinical situation could be responsible for contextual fear conditioning, a particular form of automatic associative learning[15] that is relatively impenetrable to cognitive control.[18 19] Contextual fear conditioning is defined as experiencing an aversive event in a specific context so as to result in conditioned fear to this context. It is a fundamental way in which humans and animals learn to associate context with biologically significant aversive events. This particular form of learning now appears to be deeply involved in the development of anxiety disorder after a stressful experience.[20] Fear conditioning may lead to an emotional memory trace in the absence of conscious thought or reflection, the conditioned production of fear relying on unconscious processing mediated by subcortical neural circuitry centred on the amygdala.[19 21]

The aim of the present study was to examine the mechanisms of action of midazolam on Pavlovian (classical) contextual conditioned fear. We determined the extent to which low doses of midazolam abolished the contextual conditioned fear and the extent to which any reduction in fear conditioning resulted from anxiolytic-like attenuation of the emotional component of the aversive event, impairment of memory processes or a combination of both.

Material and methods

All procedures were conducted in accordance with National Council Directive 87848 (October 19, 1989, Ministère de l'Agriculture et de la Forêt, Service Vétérinaire de la Santé et de la Protection animales) and European Communities Council Directive 86/609/EEC (November 24, 1987).

Animals

Three hundred and twenty-six naive male Long–Evans rats (CERJ, LeGenest, France), weighing 300–330 g at the beginning of the experiments, were used. All animals were housed two per cage in the colony room [mean temperature 22 (SD 2)°C], maintained on a 14-h light, 10-h dark cycle (light on at 07:00) and given food and water *ad libitum*. All animals were handled three times a week before each experiment.

Drugs

Midazolam (Roche, Basel, Switzerland) was dissolved in saline (0.9% sodium chloride) immediately before intraperitoneal injection at different doses (0, 0.37, 0.75, 1.5 and 3.0 mg kg^{-1}) in a volume of 2 ml kg^{-1} body weight.

Passive avoidance procedures

The effect of midazolam on anxiety and learning was studied using a passive avoidance apparatus that consisted of a cage with two adjacent compartments, one bright and large and the other dark and small. The bright compartment had white Plexiglas walls, measured 46 cm long, 42 cm wide and 44 cm high and was illuminated by a 25 W bulb fixed on the wall opposite the entrance to the dark box. This latter compartment had black Plexiglas walls and roof and measured 30 cm long, 15 cm wide and 15 cm high. The two compartments were separated by a guillotine door (10 cm wide and 12 cm high). The floor was made of stainless steel bars (diameter 0.6 cm) 1.8 cm apart. Scrambled electric foot-shocks could be delivered through the floor of the dark compartment.

The general procedure consisted of two trials performed 24 h apart in the two-compartment apparatus, except when otherwise specified. Rats were placed in the large, bright compartment (fearful environment), from which they could escape into the adjacent small, dark compartment (neutral environment). Latency to enter the small dark compartment was used as the measure of spontaneous fear for the bright compartment. Latency to enter the dark compartment in rats previously given shocks in this compartment was used as the measure of learning and memory for this aversive event.[22]

Assessment of drug-induced locomotor impairment

The effect of midazolam on forced and exploratory locomotion was studying using a rotarod apparatus and an 'activity cage' respectively.[23] Briefly, the rotarod apparatus consisted of an elevated (40 cm high) rotating (2 r.p.m.) bar (40 cm long, 6 cm in diameter), divided into three 11 cm long sections by four perpendicular disks (diameter 50 cm). The activity cage (45×30×30 cm) had an infrared detector (IPR124; Talco, Paris, France) placed behind a Fresnel lens and located in the roof of the cage, with which it was possible to monitor animal movement in the different sections of the cage. The signal was fed into a computer that totalled all horizontal movements (i.e. the total number of crossings from one section to the other) during periods of 5 min.

Study design

We studied the acute effects of low doses of midazolam on contextual fear conditioning, as assessed by Pavlovian (classical) fear conditioning (experiment 1) and on spontaneous escape from the innate fearful surrounding (experiment 2). [In a Pavlovian (classical) fear conditioning procedure, an initially neutral stimulus (the so-called conditioned stimulus, CS), either a discrete signal such as a tone or a light, or the experimental surrounding itself, is paired with an aversive stimulus such as a brief electrical foot-shock (the so-called unconditioned stimulus, US). When exposed later on to the CS, normal animals exhibit conditioned fear reactions, such as block of ongoing behaviour, freezing and modification of escape or avoidance latency.] In our procedure of contextual fear conditioning, the animal passively experienced mild electric foot-shocks [unconditioned stimulus (US)] in a distinctive neutral context [conditioned stimulus (CS)]. The mnemonic and/or anxiolytic mechanisms of midazolam with regard to fear conditioning were then examined by comparing the effect of midazolam on the aversively loaded event (the CS–US association) and on a non-aversive experience (pre-exposure to the CS before fear conditioning) (experiment 3). Initial exposure to the CS (with no aversive stimulus) has a deleterious effect on the subsequent CS–US association.[24] This CS-pre-exposure effect (otherwise called the latent inhibition phenomenon) is thought to depend upon information about the CS being retained at the time of pre-exposure to it.[25] Finally, we tested the possibility that midazolam could act as an affective contextual stimulus during both pre-exposure to the CS and fear conditioning (experiment 4). Additional experiments (experiments 5 and 6) were conducted in order to control for locomotor impairment and/or possible long-lasting residual actions of midazolam.

Experiment 1. Effect of midazolam on fear conditioning

On day 1 (conditioning phase), rats were enclosed for 5 min in the small, dark compartment, where they were given two mild inescapable foot-shocks (effective intensity 0.1 mA, for 5 s, 20 ms on/140 ms off) delivered 120 and 210 s after the beginning of the trial. On day 2 (testing phase), rats were placed in the large, bright compartment and latency to enter the small dark compartment was recorded (cut-off time 900 s). Rats were given a single injection of midazolam 0.37, 0.75, 1.50 or 3.00 mg kg^{-1} or saline 15 min before phase 1 (10 rats/group).

Experiment 2. Effect of midazolam on spontaneous fear

This was conducted as Experiment 1 except that rats were not subjected to foot-shocks during day 1 and a single administration of midazolam 0.37, 0.75, 1.50 or 3.00 mg kg^{-1} or saline took place 15 min before the testing phase on day 2 (10 rats/group).

Experiment 3. Comparison of the effect of midazolam on aversive and non-aversive events

Rats of two groups were initially pre-exposed to the dark compartment, where they were enclosed for 30 min; no shock was delivered during this period. All rats were injected with midazolam 0 or 3 mg kg^{-1} 15 min before this CS pre-exposure period (non-aversive event). The animals were then subjected to the conditioning phase of the fear conditioning procedure as in experiment 1, without additional treatment. Rats in two further groups were not pre-exposed to the dark compartment and were injected with midazolam 0 or 3 mg kg^{-1} 15 min before the conditioning phase (aversive event) as in experiment 1. All animals in the four groups were subjected to the testing phase of the fear conditioning procedure, as in experiment 1, without additional treatment (12 rats/group).

Experiment 4. Contextual effect of midazolam

Rats were injected with saline or midazolam 3 mg kg^{-1} 15 min before the scheduled experimental phase, as follows: On day 1, rats of two non pre-exposed groups were given midazolam (group 1) or saline (group 2) in their home cage. Rats of group 3 were given midazolam and pre-exposed for 30 min to the dark compartment; no shock was delivered during this period. Twenty-four hours later, the three groups of rats were then subjected to the conditioning and testing phases of the fear conditioning procedure, conducted as in experiment 1. All rats were injected with either saline (groups 1 and 3) or midazolam (group 2) before the conditioning phase. All animals in the three groups were given midazolam before the testing phase (14 rats/group).

Experiment 5. Delayed effect of midazolam

This experiment was conducted in order to control for a possible residual effect of midazolam (at the time of the acquisition and/or retention phases) 24 h after the injection. If observed, such an effect would hinder the interpretation of experiment 3 because rats from the pre-exposed group were given midazolam 24 h before their non-pre-exposed counterparts. All animals were subjected to the procedure described for experiment 1. All rats were injected with saline or midazolam, but at different times: 24 h before, 15 min before or 15 min after the conditioning phase (12 rats/group).

In each of the above experiments (1–5), the latency to enter (four paws) the dark compartment during the testing phase was recorded to the nearest second by an experimenter unaware of the treatment conditions.

Experiments 6A and B. Control experiments

These experiments were intended to control for the possibility that midazolam-induced locomotor impairment might have interfered with the results of the present study. In experiment 6A, 50 rats were trained in a forced locomotor activity task, using a rotarod apparatus. Rats were trained during two daily sessions until each of them reached the criterion of stability on the cylinder for at least 60 s. On the third day, rats were given midazolam 0.37, 0.75, 1.50 or 3.00 mg kg^{-1} or saline 15 min before testing. The numbers of animals staying on the cylinder at least during the first 30 s and the number of animals falling during the 60 s test session were recorded.

In experiment 6B, 50 rats were given midazolam 0.37, 0.75, 1.50 or 3.00 mg kg^{-1} or saline 15 min before being placed in the activity cage. Locomotor activity was recorded during a 5 min session test (10 rats/group).

Statistical analysis

For experiments 1–5, data were transformed ($\log_{10}$) to better approximate the normal distribution, which is necessary for

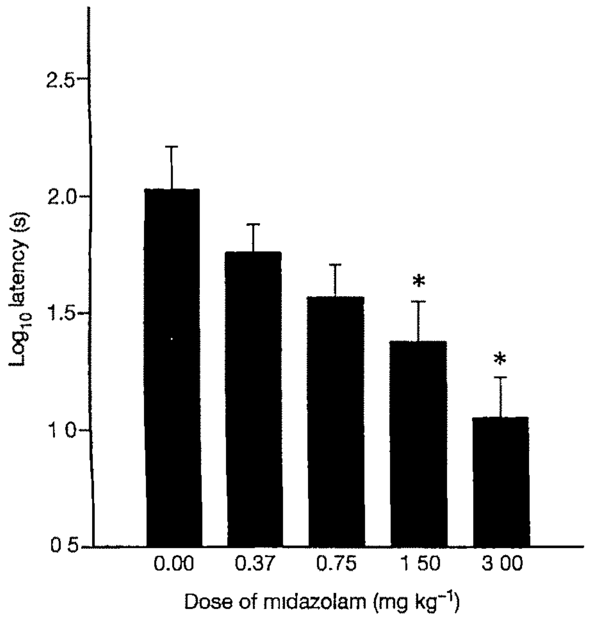


Fig 1 Midazolam-induced impairment of fear conditioning Latency ($\log_{10}$) to enter the dark compartment (mean and SEM) during the testing phase in rats given midazolam 0–3 mg kg^{-1} 15 min before the conditioning phase, during which they received two mild electric foot-shocks in the dark compartment $^{*}P<0.05$ *vs* control (Dunnett's *t* test after ANOVA)

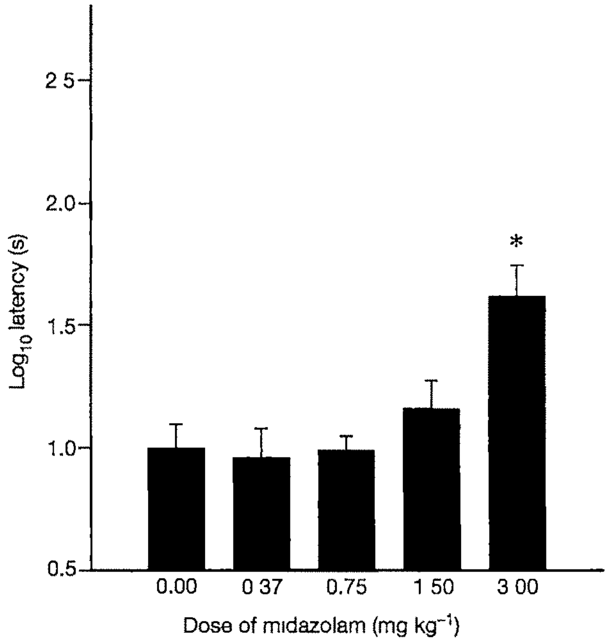


Fig 2 Midazolam-induced anxiolysis Latency ($\log_{10}$) to enter the dark compartment (mean and SEM) during the testing phase in rats given midazolam 0–3 mg kg^{-1}. No shocks were delivered in the dark compartment $^{*}P<0.05$ *vs* control (Dunnett's *t* test after ANOVA)

the use of parametric statistics. The data were subjected to one-way analysis of variance (ANOVA) followed by *post hoc* tests when needed.

Results

Experiment 1. Effect of midazolam on fear conditioning

Figure 1 shows the latency to enter the dark compartment in rats previously subjected to two shocks in the dark compartment according to the dose of midazolam they received before the conditioning phase. When placed in the large bright compartment, previously non-shocked rats usually enter the small dark compartment after about 10 s (at least 6 s). We observed increased latency (about 200 s) in control rats (saline) previously subjected to two shocks in the dark compartment, which was indicative of the fear-conditioned response. In rats given midazolam, the latency to enter the dark compartment decreased linearly to about 20 s as the dose of midazolam increased (test of linearity, $r=-0.547$; $P<0.001$; $y=-0.302x+1.893$). One-way ANOVA revealed an overall significant dose effect [$F(4,45)=5.30$; $P<0.05$]. *Post hoc* pairwise comparisons indicated that the doses of 1.5 and 3.0 mg kg^{-1} differed significantly from saline [Dunnett's $t(4,45)=3.33$, $t(4,45)=3.85$; all $P<0.05$].

Experiment 2. Effect of midazolam on spontaneous fear

Figure 2 shows the latency to enter the dark compartment in previously non-shocked rats according to the dose of midazolam they received before being placed in the large bright compartment. Control rats given saline escaped from the large bright compartment after about 10 s, confirming their spontaneous aversion to this compartment. One-way ANOVA revealed a significant main effect [$F(4, 45)=6.97$; $P<0.05$]. *Post hoc* pairwise comparisons indicated that only the 3 mg kg^{-1} dose of midazolam increased escape latency significantly [Dunnett's $t(4,45)=4.15$; $P<0.05$].

Experiment 3. Comparison of the effect of midazolam on aversive and non-aversive events

In control rats not pre-exposed to the dark compartment before receiving two shocks in this compartment, the latency to enter this compartment during the retention phase was on average 400 s (Fig. 3). This value was reduced to about 60 s in rats given midazolam 3 mg kg^{-1} before the conditioning phase (aversive event), thus replicating the results obtained in experiment 1. Saline-injected rats given a 30 min pre-exposure to the dark compartment (non-aversive event) 24 h before the conditioning phase of the fear-conditioning procedure escaped from the large compartment within 100 s; this latency was increased to 480 s in rats given midazolam 3 mg kg^{-1} before pre-exposure. A 2×2 ANOVA

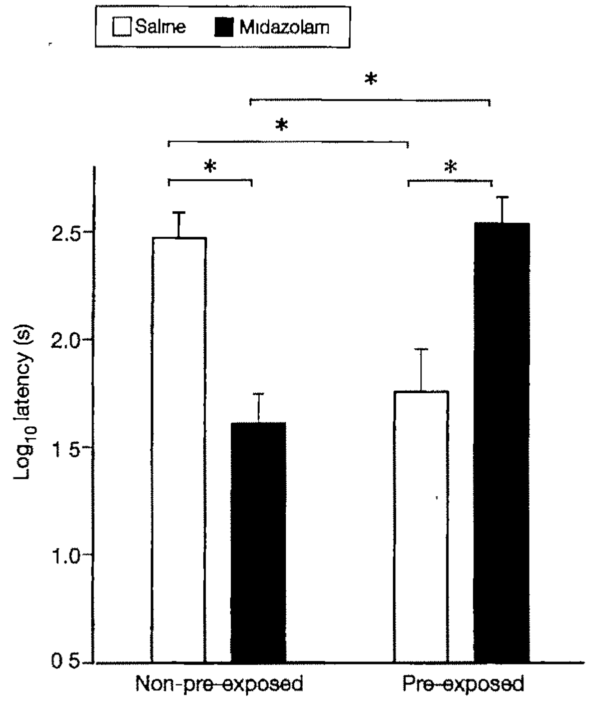


Fig 3 Comparison of the effects of midazolam on aversive (fear conditioning) and non-aversive (pre-exposure to CS) events. Latency ($\log_{10}$) to enter the dark compartment (mean and SEM) in (left) non-pre-exposed rats injected with saline (white column) or midazolam (black column) 15 min before the conditioning phase and (right) rats pre-exposed to the dark compartment 15 min after saline (white column) or midazolam (black column) On day 1, non-pre-exposed rats stayed in their home cage, whereas pre-exposed rats were placed for 30 min in the dark compartment without shocks The four groups were subjected to the conditioning and testing phases on days 2 and 3 respectively. $^*P<0.05$ (Bonferroni test after ANOVA).

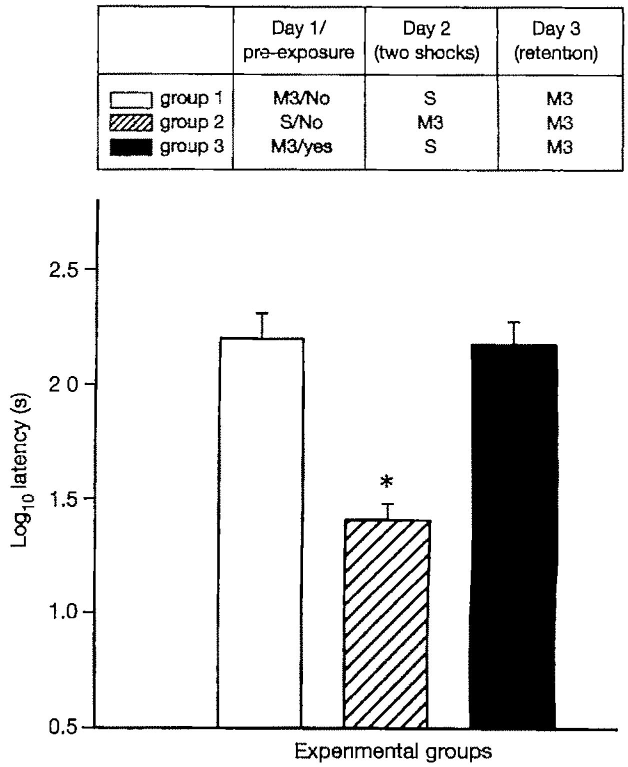


Fig 4 Midazolam did not induce state-dependent retrieval Latency ($\log_{10}$) to enter the dark compartment (mean and SEM) during the testing phase of the fear-conditioning procedure in three groups of rats given midazolam 15 min before testing The inset summarizes the experimental schedule of drug administration S=saline; M3=midazolam 3 mg kg^{-1} (see Material and methods section). $^*P<0.05$ (Bonferroni test after ANOVA)

(pre-exposure, dose) indicated a significant interaction [$F(1, 44)=29.81$; $P<0.0001$] but no main effects [both $F(1,44)<1$]. *Post hoc* pairwise comparisons using the Bonferroni test indicated that non-pre-exposed rats given saline differed from those given midazolam and from pre-exposed rats given saline. The performance of pre-exposed rats given midazolam differed from that of their saline counterparts and from those of non-pre-exposed rats given midazolam [all $t(44)>3.37$; all $P<0.05$].

Experiment 4. Contextual effect of midazolam

In group 1 animals not pre-exposed to the dark compartment before the conditioning phase, the latency to enter this compartment during the retention phase (preceded by midazolam injection) was on average 300 s (Fig. 4). This value was reduced to about 30 s in rats of group 2 given midazolam before the conditioning phase, thus replicating the results obtained in experiments 1 and 3. In group 3 animals given midazolam before 30 min of pre-exposure to the dark compartment (without shock) before the fear-conditioning procedure, the latency to enter this compartment during the retention phase (preceded by midazolam injection) was on average 300 s. This latency was in the range of the values obtained in rats not pre-exposed. This replicated the results obtained in experiment 3. One-way ANOVA (group) revealed a significant main effect [$F(2, 38)=24.22$; $P<0.0001$]. *Post hoc* pairwise comparisons using the Bonferroni test indicated that only group 2 animals given midazolam 15 min before the conditioning phase exhibited a significant reduction in latency to move out of the bright compartment compared with groups 1 and 3 [$t(38)=6.05$ and 6.71 respectively; all $P<0.05$].

Experiment 5. Delayed effect of midazolam

Whether the injection was given before or after the conditioning phase, rats given saline exhibited a similar latency to enter the dark compartment during the testing phase (Fig. 5). These values were in the range of those obtained in control rats in experiments 1 and 3. A 3×2 ANOVA (injection time, treatment) indicated a significant injection time effect [$F(2, 66)=14.34$; $P<0.0001$], no treatment effect [$F(1, 66)=3.33$] and a significant interaction [$F(2, 66)=8.04$; $P<0.001$]. *Post hoc* pairwise comparisons using the Bonferroni test indicated that only rats given

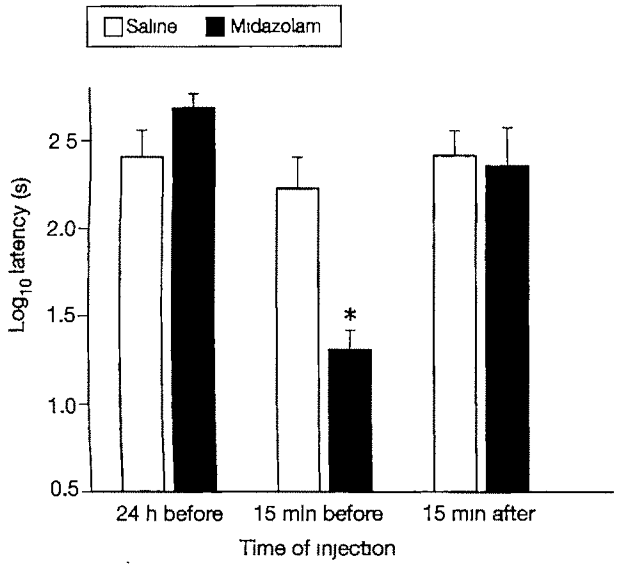


Fig 5 Temporal contiguity for midazolam effect on fear conditioning Latency ($\log_{10}$) to enter the dark compartment (mean and SEM) during the testing phase for groups injected with saline (white columns) or midazolam 3 mg kg^{-1} (black columns) 24 h before, 15 min before or 15 min after the conditioning phase $^{*}P<0.05$ (Bonferroni test after ANOVA)

midazolam 3 mg kg^{-1} 15 min before the conditioning phase exhibited a significant reduction in latency to move out of the bright compartment compared with their associated controls [$t(66)=4.20$; $P<0.05$].

Experiments 6A and B. Control experiments

Rats given midazolam 0–3 mg kg^{-1} exhibited no alteration of performance on the rotarod test. All the animals stayed on the bar for more than 30 s; during the 60 s test, the numbers of falls were 0, 1, 0, 1 and 1 for the five groups respectively ($\chi^2=2.09$; not significant) (experiment 6A). The mean (SEM) activity scores were 229 (10), 220 (9), 244 (7), 226 (12) and 227 (11) units for rats receiving saline and midazolam 0.37, 0.75, 1.5 and 3 mg kg^{-1} respectively. One-way ANOVA (dose) showed no overall effect [$F(4, 45)=0.85$] (experiment 6B).

Discussion

The present study provides evidence that midazolam impairs conditioned contextual fear conditioning by acting on pure mnemonic rather than emotional processes or a combination of the two. Such an effect was observed at low doses of midazolam (1.5 and 3.0 mg kg^{-1}), at which spontaneous or forced motor activities were unaffected, the hypnotic dose being above 30 mg kg^{-1} intraperitoneally in our experimental conditions.[17]

Indeed, rats subjected to inescapable electric foot-shocks (unconditioned stimulus, US) in the dark side (contextual conditioned stimulus, CS) of a two-compartment box exhibited a clear increase in latency to enter this compartment on a subsequent session, an effect that reflects the acquisition of the CS–US association. When administered before the shock session, midazolam dose-dependently counteracted this effect (experiment 1). Such a disruption may rely on drug-induced anterograde amnesia, but could also have resulted from an anxiolytic effect by the time of acquisition. Low doses of midazolam increased the latency to escape from the bright compartment, which is indicative of an anxiolytic effect in rodents (experiment 2) This increase in latency cannot be attributed to any locomotor impairment, because spontaneous or forced motor activities were unaffected in the same range of doses (experiments 6A and B). Moreover, conditioned fear was altered (i e. the latency to enter the dark compartment during the retention test was shortened) when midazolam was administered 15 min before the shock session but not when the injection took place 24 h before or 15 min after the conditioning phase (experiment 4). Therefore, residual activity of midazolam at the time of the retention test cannot account for the reduction in the fear reaction observed in experiment 1. However, one could argue that midazolam reduced the perception of the aversive unconditioned stimulus (shocks) by an antinociceptive effect. There is clear evidence in the literature that midazolam is totally devoid of any analgesic effect.[26 27] Similarly, preliminary data obtained in our laboratory showed no effect of midazolam 3 mg kg^{-1} on the threshold of the shock intensity to elicit a jump in rats compared with saline administration.

Because learning an aversive effect occurs in an emotional frame, the reduction in conditioned fear of the context by midazolam may result from changes in the emotional/affective aspects of the situation at the learning stage, the mnemonic processes or the combination of both phenomena.[8 10] Midazolam could have disrupted the establishment of the CS–US association through an anxiolytic-related reduction in the emotional part of this aversive event. If midazolam disrupts the CS–US association through mnemonic processes, it should exert this effect whether or not the event that is to be conditioned has an aversive component. The CS pre-exposure procedure (see Material and methods) was used to control for such a possibility (experiment 3). Thirty minutes of pre-exposure to the dark box (CS alone) before the CS–US association (conditioning phase) resulted in a reduction in the latency to enter this compartment during the retention phase. Pre-exposure to the stimulus that was to be conditioned had a deleterious effect on the subsequent acquisition and/or expression of the CS–US association. In rats given midazolam before CS pre-exposure, latency to enter the dark compartment during the retention phase of the fear conditioning procedure was lengthened to a value similar to that observed in control non-pre-exposed rats. Pre-exposure to the dark compartment was a non-aversive experience compared with the conditioning phase, during which rats received uncontrollable shocks. The administration of midazolam resulted in total suppression of the effect of CS pre-exposure on fear conditioning. This shows that the midazolam-induced alteration in fear conditioning was more likely to be accounted for by disruption of memory formation rather than by an anxiolytic-like reduction in the emotional component of the CS–US (shocks) association or by reduction in the perception of the aversive unconditioned stimulus. Another benzodiazepine, chloradiazepoxide, has been shown to suppress the CS pre-exposure effect on fear conditioning in rats, but such an effect was observed only at high sedative doses.[28 29]

However, it could be argued that midazolam acted as a context alone during both the pre-exposure and the conditioning phase.[30] Because the retention phase was performed with no additional treatment in experiments 1 and 3, a drug-to-no-drug state change could account for the observed effects of midazolam on both the CS pre-exposure and fear conditioning. It has been reported regularly that drugs such as benzodiazepines might induce a state-dependent retrieval phenomenon that is seen only when the retention test is performed with drug.[31–33] Moreover, because midazolam displays affective properties (pleasant affective state),[17] one could argue that midazolam acted as a pleasant contextual stimulus during the pre-exposure phase, changing a non-aversive experience (pre-exposure) to a pleasant experience. Such a shift of affective context between the pre-exposure and testing phases has been shown to impair the effect of pre-exposure on fear conditioning.[34] In experiment 4, we found that the midazolam dose of 3 mg kg^{-1} totally suppressed the deleterious effect of CS pre-exposure on subsequent fear conditioning, even when the testing phase was performed in a 'midazolam state'. This replicated the results obtained in experiment 3. At the same time, midazolam disrupted the fear conditioning in rats given midazolam before both the acquisition and the retention phase, as observed in experiments 1 and 3. These data show clearly that a shift of context or a state-dependent retrieval phenomenon cannot be responsible for the observed effects of midazolam on the CS pre-exposure effect and on fear conditioning.

One of the principal goals of using midazolam in clinical practice is to produce amnesia for untoward events.[35–37] In humans, it has been demonstrated that midazolam induces anterograde amnesia, depending on the dose.[12 15 38–40] However, the work mentioned above studied the memory (implicit or explicit) for non-emotionally loaded information (words, pictures) or the explicit recall of untoward events (pain, fear) in patients in whom a state of excessively deep sedation was often produced to obtain some-amnesic like effect. Midazolam-induced amnesia, independently of a reduction in awareness, has been described in particular forms of learning: memory (implicit or explicit) for non-emotionally loaded information,[15 38 41] procedural learning in humans[42] and operant learning in animals (in which the animal learns what occurred in the environment in response to its behaviour).[26 43] These forms of learning do not reflect exactly the mechanism of learning in patients passively experiencing an aversive event. It was for this reason that we examined the effects of low doses of midazolam on Pavlovian fear conditioning in animals passively experiencing an aversive stimulus. Our findings in rats suggest that midazolam might suppress the subsequent conditioned fear resulting from an aversive event occurring under conscious sedation (when verbal contact is maintained in humans).

In conclusion, low doses of midazolam (less than 10% of the hypnotic dose) were able to prevent the expression of conditioned fear after an aversive event in rats. The main mechanism by which midazolam acts on such contextual fear conditioning relies on its memory effect. The anxiolytic effect of midazolam in a fearful context plays a negligible role compared with its effect on memory processes. The mnemonic processes (acquisition, storage or retrieval) involved in the disruption of contextual fear learning by midazolam are currently under investigation.

Acknowledgements

We thank Lilianne Manning, John M Pearce and Marie-Hélène Thiébot for their helpful comments during the preparation of this manuscript Financial support for this research was provided by SFAR (contrat de recherche 1997), MENRT-INSERM 1999/2000 'Soutien aux Sciences du Vivant' au sein de l'Institut Fédératif de Recherches Neurosciences 37 and Université Louis Pasteur 'Appel à projets Exceptionnels 2000' This work was presented in part at the IVth symposium on Memory and Awareness in Anaesthesia, London, July 1998.

References

1 Tinnin L. Conscious forgetting and subconscious remembering of pain. *J Clin Ethics* 1994; **5**: 151–152

2 Andrade J. Learning during anaesthesia: a review *Br J Psychol* 1995; **86**: 479–506

3 Ghoneim MM, Block RI. Learning and memory during general anesthesia: an update. *Anesthesiology* 1997; **87**: 387–410

4 Osterman JE, van der Kolb BA. Awareness during anesthesia and posttraumatic stress disorder. *Gen Hosp Psychiatry* 1998; **20**: 274–81

5 Ghoneim MM, Mewaldt SP Benzodiazepines and human memory: review. *Anesthesiology* 1990; **72**: 926–38

6 Lister RG. The amnesic action of benzodiazepines in man. *Neurosci Biobehav Rev* 1985; **9**: 87–94

7 Thiébot MH. Some evidence for amnesic-like effects of benzodiazepines in animals. *Neurosci Biobehav Rev* 1985; **9**: 95–100

8 Borde N, Krazem A, Jaffard R, Beracochea DJ. Memory deficits following diazepam administration in mice: evidence for a time-dependent retrieval impairment. *Psychobiology* 1997; **25**: 202–9

9 Curran HV. Benzodiazepines, memory and mood: a review. *Psychopharmacology* 1991; **105**: 1–8

10 Blaney PH. Affect and memory: a review. *Psychol Bull* 1986; **99**: 229–46

11 Eich E. Searching for mood dependent memory. *Psychol Sci* 1995; **6**: 67–75

12 Veselis B, Reinsel R, Alagesan R, Heino R, Bedford R. The EEG as a monitor of midazolam amnesia: changes in power and topography as a function of amnesic state. *Anesthesiology* 1991; **74**: 866–74

13 Polster MR, McCarthy RA, O'Sullivan G, Gray PA, Park GR. Midazolam-induced amnesia: implications for the implicit/explicit memory distinction. *Brain Cogn* 1993; **22**: 244–65

14 Thomas-Anterion C, Koening O, Navez M, Laurent B. Midazolam effects on implicit and explicit memory processes in healthy subjects *Psychopharmacology* 1999; **145**: 139–43

15 Hirshman E, Passannante A, Arndt J. The effect of midazolam on the modality-match effect in implicit memory. *Brain Res Cogn Brain Res* 1999; **7**: 473–9

16 Salonen M, Onaivi ES, Maze M. Dexmedetomidine synergism with midazolam in the elevated plus-maze test in rats. *Psychopharmacology* 1992; **108**. 229–34

17 Pain L, Oberling P, Sandner G, Di Scala G. Effect of midazolam on propofol-induced pleasant affective state as assessed by place conditioning paradigm in rats. *Anesthesiology* 1997; **87**: 935–44

18 Pearce JM, Bouton ME. Theories of associative learning in animals. *Annu Rev Psychol* 2001; **52**: 111–39

19 Ohman A, Mineka S. Fears, phobias, and preparedness: toward an evolved module of fear and fear learning. *Psychol Rev* 2001, **3**: 483–522

20 Bouton ME, Mineka S, Barlow DH. A modern learning theory perspective on the etiology of panic disorder. *Psychol Rev* 2001; **108**: 4–32

21 Davis M. The role of the amygdala in conditioned fear. In: Aggleton JP, ed. *The Amygdala Neurobiological Aspects of Emotion, Memory and Mental Dysfunction.* New York: Wiley-Liss 1992; 255–305

22 Mora PD, Fouquet N, Oberling P, Gobaille S, Graeff FG, Sandner G. A neurotoxic lesion of serotoninergic neurons using 5,7-dihydroxytryptamine does not disrupt latent inhibition in paradigms sensitive to low doses of amphetamine *Behav Brain Res* 1999; **100**: 167–75

23 Pain L, Oberling P, Launoy A, Di Scala G. Effect of non sedative doses of propofol on an innate anxiogenic situation in rats. *Anesthesiology* 1999; **90**: 191–6

24 Grahame NJ, Barnet RC, Gunther LM, Miller RR. Latent inhibition as a performance deficit resulting from CS–context associations. *Anim Learn Behav* 1994; **22**: 395–408

25 Oberling P, Gosselin O, Miller RR. Latent inhibition in animals as a model of acute schizophrenia: a reanalysis. In: Haug M, Whalen RE, eds. *Animal Models of Human Emotion and Cognition.* Washington DC. American Psychological Association, 1999, 87–102

26 Harris JA, Westbrook RF. Midazolam impairs the acquisition of conditioned analgesia if rats are tested with an acute but not a chronic noxious stimulus *Brain Res Bull* 1996; **39**: 227–33

27 Zacny JP, Coalson D, Young C *et al.* A dose–response study of the effects of intravenous midazolam on cold pressor-induced pain. *Anesth Analg* 1995; **80**: 521–5

28 Feldon J, Weiner I. Abolition of the acquisition but not the expression of latent inhibition by chlordiazepoxide in rats *Pharmacol Biochem Behav* 1989, **32**: 123–7

29 Lacroix L, Spinelli S, Broersen LM, Feldon J. Blockade of latent inhibition following pharmacological increase or decrease of GABA$_A$ transmission. *Pharmacol Biochem Behav* 2000; **4**: 893–901

30 Harris JA, Westbrook RF. Contextual control over the expression of fear in rats conditioned under a benzodiazepine. *Psychopharmacology* 2001; **156**: 92–7

31 Colpaert FC. Amnesic trace locked into the benzodiazepine state of memory. *Psychopharmacology* 1990, **102**: 28–36

32 Bouton ME, Kenney FA, Rosengard C. State-dependent fear extinction with two benzodiazepine tranquilizers. *Behav Neurosci* 1990; **104**: 44–55

33 File SE, Goodall EM, Mabbutt PS, Harris A, Skelly AM. State-dependent retrieval and midazolam *Human Psychopharmacol* 1993; **8**: 243–51

34 Killcross S, Balleine B. Role of primary motivation in stimulus preexposure effects. *J Exp Psychol Anim Behav Process* 1996; **22**: 32–42

35 Nadin G, Coulthard P Memory and midazolam conscious sedation. *Br Dent J* 1997; **183**: 399–407

36 Wagner BK, O'Hara DA, Hammond JS. Drugs for amnesia in the ICU. *Am J Crit Care* 1997, **6**: 192–201

37 Henderson A, Dipplesman J, Miller J. Failure of intravenous low dose to influence memory recall in drug paralysed post-operative patients sedated with papaveretum. *Aust Crit Care* 1994; **7**: 22–4

38 Glass PS, Bloom M, Kearse L, Rosow C, Sebel P, Manberg P. Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. *Anesthesiology* 1997; **86**. 836–47

39 Thompson JM, Neave N, Moss MC, Scholey AB, Wesnes K, Girdler NM. Cognitive properties of sedation agents: comparison of the effects of nitrous oxide and midazolam on memory and mood. *Br Dent J* 1999; **187**: 557–62

40 Ghoneim MM, Block RI, Ping ST, el-Zahaby HM, Hinrichs JV The interactions of midazolam and flumazenil on human memory and cognition. *Anesthesiology* 1993; **79**. 1183–92

41 Veselis RA, Reinsel RA, Feshenko VA, Wronski M The comparative amnestic effects of midazolam, propofol, thiopental, and fentanyl at equisedative concentrations. *Anesthesiology* 1997; **87**: 734–6

42 Rammsayer TH, Rodewald S, Groh D. Dopamine-antagonistic, anticholinergic, and GABAergic effects on declarative and procedural memory functions. *Brain Res Cogn Brain Res* 2000; **9**: 61–71

43 Salinas JA, Dickinson-Anson H, McGaugh JL Midazolam administered to rats induces anterograde amnesia for changes in reward magnitude. *Behav Neurosci* 1994, **108**: 1059–64

British Journal of Anaesthesia 89 (4): 622–32 (2002)

BJA

REVIEW ARTICLE

Pathophysiology and clinical implications of perioperative fluid excess

K. Holte[1]*, N. E. Sharrock[2] and H. Kehlet[1]

[1]*Department of Surgical Gastroenterology, Hvidovre University Hospital, DK-2650 Hvidovre, Denmark.*
[2]*Department of Anesthesiology, Hospital for Special Surgery, New York, USA*
**Corresponding author*

Br J Anaesth 2002; **89**: 622–32

Keywords: complications, hypervolaemia; fluid balance; safety, techniques

The practice of perioperative fluid therapy is variable, ranging from 'high volume' to 'dry' regimen. A review of the data on the effect of 'high volume' perioperative fluid therapy suggests that the resulting overhydration may have deleterious effects on cardiac and pulmonary function, and on recovery of gastrointestinal motility (postoperative ileus), tissue oxygenation, wound healing and coagulation. These observations call for randomized studies of the effects of 'high' *vs* 'low' volume replacement therapy on postoperative morbidity, in order to establish evidence-based guidelines for perioperative fluid management.

Perioperative fluid replacement has been, and still is, the focus of much debate. This debate has primarily focused on the various types of fluid components available for replacement therapy, and not on the actual amount of fluid administered.

The principles of perioperative fluid therapy were fostered in the late 1950s and early 1960s. Recommendations for restricted fluid regimen came primarily from Francis Moore,[85] arguing that the net effect of the obligatory metabolic–endocrine response to trauma, which is conservation of water and sodium, implied restriction in fluid delivery. In contrast, Tom Shires[129] postulated a decrease in extracellular volume after surgery, due to internal redistribution of fluids, the 'third space' losses, and advocated replacement of these losses by additional fluid infusion. These considerations were supported by studies during the Korean War, where large amounts of fluid were administered in trauma patients with improved survival, thereby also influencing the recommendations for elective surgery.[6] The concept of resuscitation in order to achieve supranormal circulatory function was developed in the 1970s and 1980s by Shoemaker,[130] and obtained primarily by the use of fluid infusions and inotropes. Clinical practice has largely been influenced by Shires' recommendations and it has not been uncommon to see very large amounts of fluid administered in elective surgical procedures, way in excess of the actual losses. This is especially the case in major aortic or abdominal surgery, where 4–6 litres or more of intraoperative fluid substitution (apart from replacement of blood losses) have been given,[22 35 66 134] or in peripheral vascular surgery with more than 6 litres of fluid administered within surgery and the first 24 h after surgery, despite a minimal blood loss.[19] Up to 4 litres of fluid have been administered within the first 24 h in patients undergoing laparoscopic cholecystectomy.[36] In contrast, in thoracic surgery, relatively 'dry' regimen have been considered to be beneficial, due to the association between the amount of administered fluid and the development of post-pneumonectomy pulmonary oedema.[52 133 149]

Several issues in perioperative management may account for the administration of excessive amounts of fluid, including concern about preoperative fluid deficits (dehydration, primarily derived from prolonged preoperative fasting and bowel preparation), attempts to support the circulation and cardiac function after general and regional anaesthesia, attempts to control the circulation postoperatively, administration of crystalloid or colloid to avoid blood transfusion, preservation of urine output and preservation of a high CVP from fluid infusion.

Administration of excess fluid may cause several problems after surgery. The resulting increased demands on cardiac function, due to an excessive shift to the right on the Starling myocardial performance curve, may potentially increase postoperative cardiac morbidity. Fluid accumulation in the lungs may predispose patients to pneumonia and respiratory failure. The excretory demands of the kidney are increased, and the resulting diuresis may lead to urinary

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Table 1 Hormonal responses to surgery and fluid overload

Hormone	Response to surgery (Reference numbers)	Response to overload	Effect on fluid distribution
Aldosterone	Increase (27, 143)	Decrease (142)	Sodium and fluid retention, potassium excretion
Antidiuretic hormone	Increase (27, 143)	Decrease (48)	Water retention
Renin–angiotensin II	Increase (27, 143)	Decrease (2–4, 94, 142)	Sodium and fluid retention; potassium excretion
Atrial natriuretic peptide	Increase or no change (59, 62, 63)	Increase (54, 68, 119, 146)	Diuretic, natriuretic

retention mediated by the inhibitory effects of anaesthetics and analgesics on bladder function. Gastrointestinal motility may be inhibited, prolonging postoperative ileus. Excess fluid may decrease tissue oxygenation with implications for wound (anastomotic) healing. Finally, coagulation may be enhanced with crystalloids, which may predispose patients to postoperative thrombosis.

In this review we summarize the pathophysiology of perioperative fluid excess, and review the effects of it on organ function and the potential clinical implications. We discuss the aspects of fluid management in regional anaesthesia, and the implications of immobilization on fluid homeostasis. We focus on perioperative fluid therapy in elective surgical procedures. We do not intend to present recommendations on fluid replacement strategies, or to discuss the various components available for fluid replacement or the current methods of monitoring fluid balance. Furthermore, we do not intend to discuss the treatment options for hypovolaemia or the use of i.v. fluids in critically ill patients.

Surgical stress and fluid responses

Water makes up 60% of total body weight, one third of it being extracellular fluid volume (ECV) (interstitial fluid and plasma), and two thirds being intracellular volume. Transportation of fluid between the body compartments is regulated by the Starling equilibrium, the decisive variables being differences in hydrostatic and colloid osmotic pressure, and specific permeability coefficients. In response to surgery, serum colloid osmotic pressure is decreased,[64 125] which is primarily caused by increased capillary permeability, resulting in fluid shifts from the vascular bed to the interstitial fluid.[60 125] Dilution secondary to crystalloid infusions may also contribute.[71] In addition, as a physiological response to a decrease in intravascular pressure, fluid movement from the extravascular to the intravascular space occurs, as demonstrated in a human volunteer study where experimental hypovolaemia led to fluid movements from tissue to blood.[74]

Changes in ECV after surgery have been much debated, and fluid replacement today is greatly influenced by Shires,[127 129] who postulated a decrease in *functional* (i.e. exchangeable) ECV after elective surgical procedures and haemorrhagic shock. According to Shires, surgical trauma *per se* (without administration of fluids) led to a decrease in functional ECV, which was proportional to the degree of surgical trauma.[129] Shires primarily explained the decrease in functional ECV by sequestration of fluids within the traumatized area or expansion of the intracellular volume, and therefore advocated replacement of these losses with additional saline infusions.[110 128 129] However, these observations have been contradicted by several other investigators reporting unchanged,[40 65 91 138] or even increased,[21 112] ECV in postoperative patients, and studies in major surgery suggest that ECV expansion may correlate with intraoperative fluid administration.[93 112] Thus, a positive fluid balance of 3 litres was associated with unchanged ECV, but a smaller or larger fluid excess with a decrease or increase in ECV, respectively.[93] In other studies, intracellular volume has been found to be decreased after surgery (intracellular dehydration).[31] Difficulty in obtaining accurate measurements of the fluid phases is generally recognized,[86] however, and may relate to the use of isotopes with different volumes of distribution, different equilibrium times and general changes in equilibrium times and distribution volumes as a consequence of the surgical trauma.

Therefore, despite 30 yr of research, perioperative ECV changes have not been clarified. However, the present data suggest that the magnitude of ECV decrease suggested by Shires may not be accurate, partly because the type of surgery, anaesthesia and perioperative fluid management were not standardized. Further studies are required to assess ECV changes after surgery with standardized regimen.

Surgery elicits a stress response of combined endocrine and inflammatory origin.[27 143] Several of the hormones involved in this response may exert a potentially profound influence on the distribution of body fluids (Table 1). Generally, the endocrine response to surgical trauma leads to conservation of sodium and water and to excretion of potassium, the principal mediators being antidiuretic hormone (ADH), aldosterone and the renin–angiotensin II system.[27 143] The increased ADH secretion leads to enhanced water reabsorption in the kidney, resulting in a postoperative decrease in diuresis and a decrease in plasma concentrations of sodium. The increased secretion of aldosterone and renin leads to conservation of sodium and excretion of potassium. Several other mediators, enhanced by the surgical stress, may influence the distribution of fluid. Thus, increased cortisol secretion, an obligatory stress response, may be of major importance in the control fluid homeostasis, primarily through permissive actions to maintain capillary integrity.[117] In addition, the cortisol-induced inhibition of excessive inflammatory activity response to trauma may reduce postoperative fluid shifts.[117] Atrial natriuretic peptide (ANP) secretion in response to surgery is unclear because ANP secretion may be increased in older patients, in contrast to unchanged ANP levels in younger patients.[59,62,63] ANP may induce natriuresis, diuresis and inhibition of aldosterone and ADH secretion.[90] Furthermore, inflammatory mediators, like IL-6, TNF, substance-P and bradykinin may act as vasodilators and increase capillary permeability. The release of these inflammatory mediators is proportional to the magnitude of the surgical trauma.[58] The hormonal release in response to surgical trauma therefore generally induces a shift toward water and sodium retention, while the excretion of potassium is increased, paralleling the increase in catabolism.

Studies in healthy volunteers make it possible to investigate the individual factors of importance in perioperative fluid balance, independently of the surgical trauma; the surgically induced factors, such as increased capillary permeability, are eliminated when studying volunteers. In order to investigate the effects of the stress responses seen after surgery *per se*, continuous infusions (>2 days) of cortisol/hydrocortisone, glucagon and epinephrine have, in three studies in healthy volunteers, been found to decrease sodium excretion and increase potassium excretion.[10,11,140] Furthermore, in two of these studies a weight gain of approximately 0.4 and 1.7 kg, respectively, was seen.[11,140] These findings were not modified by the concomitant infusion of an inflammatory agent (ethiocholanolone),[140] despite an increased acute phase protein response. These results demonstrate that activation of the stress response leads to fluid retention.

In contrast, several of the stress responses to injury may be influenced by fluid volume expansion *per se*. Increased capillary permeability leading to increased filtration of plasma proteins was seen after infusion of Dextran 1000 ml or 360 ml of albumin in healthy volunteers.[96] The inhibition of aldosterone secretion with fluid infusions is well established, both in healthy volunteers and surgical patients.[142] Attenuation of ADH secretion seems only to occur with high volume fluid infusions of about 50 ml min^{-1},[48] while lower infusion volumes of 15 ml min^{-1} [12] or 15 ml kg^{-1} h^{-1} [132] did not attenuate it. ANP secretion is increased after saline infusion in healthy volunteers,[54,68,119,146] but the response is transient and occurs within and immediately after the infusion. The renin–angiotensin II secretion is inhibited with fluid administration, and evidence suggests that the renin–angiotensin II system is of major importance in the excretion of a fluid overload.[2-4,29,94,142] However, there is no systematic evaluation of ANP and renin responses to fluid regimen in surgical procedures.

A large fluid volume therefore influences several of the hormonal responses to injury in surgical patients (decrease in ADH, decrease in aldosterone), while the effect of fluid administration on other hormones known to be increased postoperatively (renin and ANP) has only been systematically evaluated in healthy volunteers. Thus, the effects of perioperative fluid administration on the stress responses to surgery are unclear and need to be evaluated in clinical studies comparing high *vs* low fluid regimen.

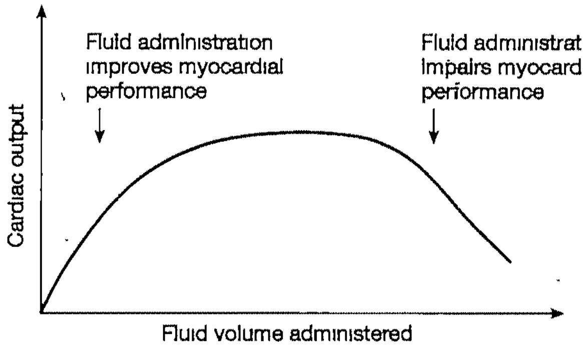


Fig 1 Effects of perioperative fluid therapy on the Starling myocardial performance curve.

Organ dysfunction and postoperative complications

Cardiac function and morbidity

The physiological relationship between cardiac filling and cardiac output is described in Starling's myocardial performance curve (Fig. 1). The curve describes the functional consequences of alterations in preload on cardiac output, and is the rationale behind improvement of cardiac output by volume administration. Until a certain point, volume expansion leads to increased cardiac output due to increased end-diastolic ventricular filling. Beyond that point, increased end-diastolic volume will lead to a decrease in cardiac output due to depression of ventricular function. Measurements of cardiac responses (primarily cardiac output) in response to a fluid load have been used to define the optimal ventricular filling pressures (evaluated by pulmonary artery catheter measurements).[15,77,141] However, although increases in end-diastolic filling pressures may increase cardiac output, the effects on other aspects of ventricular function, such as the ejection fraction and end-systolic pressure, may occur at different filling pressures.[76] This makes determination of the effect of the optimal end-diastolic filling pressure on overall cardiac function difficult by intravascular catheter measurements. In one study during cardiac surgery, plasma volume expansion to achieve maximal ventricular stroke volume assessed by oesophageal Doppler measurements (on average 900 ml crystalloid and 1400 ml colloid) led to a significantly better perfusion of the gastrointestinal mucosa and a significant decrease in major postoperative complications (major infections, stroke, paralytic ileus, respiratory failure and death).[89] Furthermore, in a randomized study in 40 patients undergoing surgery for hip fracture, intraoperative fluid infusion to maximize ventricular stroke volume (on average 750 ml of colloid infusion) led to improvements in postoperative mobilization and hospital stay.[131] In these studies, however, patients did not receive excessive fluid, but were adequately resuscitated, thus optimizing their position on the Starling curve. In a prospective study of 4059 patients undergoing major elective non-cardiac surgery, patients who underwent perioperative right-heart catheterization had a threefold increase in the incidence of major postoperative cardiac events (ischaemic events, arrhythmia or heart failure) compared with patients who were not catheterized (15.4 *vs* 3.6%).[104] The catheterized patients were also given more fluids (net fluid balance of 3.2 *vs* 2.0 litres), and the authors suggested that the adverse outcome was due, at least in part, to excessive fluid administration. However, since fluid administration was determined by right-heart catheterization and not investigated *per se*, these results are inconclusive with regard to the potentially deleterious effects of fluid overload.

Fluid loading to optimize cardiac function should therefore be guided by the Starling curve, and may have beneficial effects on postoperative organ function. Theoretically, perioperative infusions of excessive amounts of fluid may increase cardiovascular demands and morbidity. However, this has not been specifically investigated in randomized studies comparing low *vs* high fluid regimen.

Pulmonary function and complications

Removal of excess fluid from the alveolar space is also driven by active sodium transport, and not only, as previously believed, by differences in hydrostatic and colloid osmotic pressures.[79] The sodium channels involved may potentially be upregulated by catecholamines and glucocorticoids as well as by proinflammatory cytokines, all of which are increased in response to surgery,[79] and modified by fluid administration as already discussed. This may account for the conflicting evidence from previous studies examining the relations between fluid administration and pulmonary oedema.[52] In response to an i.v. saline load of 22 ml kg^{-1} in healthy volunteers, functional residual capacity decreased by 10% and diffusing capacity by 6%, both of which had not returned to normal 40 min after the infusion (later measurements were not made).[45] In another study in five volunteers, infusion of 1 litre of isotonic saline led to small decreases in total lung capacity (about 0.25 litres) and forced vital capacity (about 0.1 litres), which returned to normal after 1 h. Infusion of 2 litres of normal saline led to a similar decrease in the same variables; the effects were still present 1 h after the infusion, but recovered after subsequent furosemide administration.[23]

The incidence of pulmonary oedema after lung surgery may be as high as 12–15%.[52] The pathogenesis is unclear, but impaired lymphatic drainage, the extent of surgical injury and one-lung ventilation may be of importance. The volume of fluids administered during the perioperative course has been found to correlate with the development of post-pneumonectomy pulmonary oedema.[133 137 149] In retrospective studies, a 24-h fluid replacement of >3 litres,[97] and intra-operative fluid load of 2000 ml or more,[95] were predictive factors for the development of post-pneumonectomy pulmonary oedema. However, in some retrospective studies, post-pneumonectomy pulmonary oedema was not related to the volume of administered fluids.[135 139] These findings have not been investigated in randomized clinical trials comparing high *vs* low fluid regimen.

In non-thoracic surgery, excessive fluid administration may also result in adverse respiratory function. In 13 patients, the development of lung oedema after various elective surgical procedures correlated with a net fluid retention exceeding 67 ml $kg^{-1}day^{-1}$.[5] In a randomized study between general and regional anaesthesia in peripheral vascular surgery with minimal blood loss, patients received more than 6 litres of crystalloid infusion within 24 h after surgery.[19] Despite the low surgical stress, the overall pulmonary morbidity was exceptionally high, since 10% of the patients developed respiratory failure.[19]

Renal function and urinary retention

Since the kidneys are responsible for excretion of the majority of administered fluids, renal functional demands are increased in a state of fluid overload. In addition, the hormonal responses after injury may decrease water and sodium excretion, primarily due to the enhanced secretion of ADH, aldosterone and renin.[27] The glomerular filtration rate (GFR) was significantly increased with administration of 210–300 ml m^{-2} h^{-1} of a balanced salt solution compared with 75–200 ml m^{-2} h^{-1} during surgery.[47] In 53 patients undergoing major vascular surgery, GFR was also found to increase after surgery, with cumulated fluid balances of 2.2–6 litres, explained by an increase in ECV, renal plasma flow or both.[92] On the other hand, several studies in healthy volunteers have demonstrated that excretion of an acute saline overload (22 ml kg^{-1}) takes approximately 2 days.[28–30] Of 20 burn patients receiving an overload of 3–7 litres, only ten had excreted the overload within 1 week.[39] The prolonged fluid elimination has been found to correlate with elevated levels of urodilatin (an ANP-related polypeptide), and decreased levels of renin in healthy volunteers.[28 29]

General anaesthesia may exert an inhibitory effect on renal haemodynamics and function, reflected in the depression of GFR, urinary volume and sodium excretion.[26] However, the relationship between haemodynamics and renal function is not clear. Thus, in 987 patients undergoing total hip replacement with hypotensive epidural anaesthesia, in which intraoperative fluid averaged 1200 ml, renal dysfunction was not present.[124]

Without fluid load, urine output is negligible under general anaesthesia.[25] Consequently, fluid is generally administered to maintain a higher urine output, based upon a fear that renal failure may develop if urine flow is low.[126] However, there is no evidence of an association between low urine output *per se* and the development of renal failure (providing hypovolaemia is not present), as demonstrated in 137 consecutive patients undergoing abdominal aortic revascularization, where intraoperative urine output did not predict postoperative renal function.[1] Optimal preoperative fluid loading using the Starling curve (left side of the Starling curve, Fig. 1) has not been proven to prevent postoperative renal insufficiency.[108] In 100 critically ill patients, development of oliguria was not related to the amounts of fluid administered,[147] and it occurred in the presence of normal blood urea and creatinine. In 24 patients undergoing major neck surgery and randomized to 'generous' or 'restricted' fluid regimen, intraoperative urine output in the 'restricted' fluid group was 0.4 ml kg^{-1} h^{-1} compared with 1.33 ml kg^{-1} h^{-1} in the 'generous' fluid group.[106] Nevertheless, postoperative renal function remained normal in both groups. In 14 adult recipients of living-donor kidneys, who were randomly assigned to high fluid replacement (urine output plus 30 ml h^{-1}) or low fluid replacement (constant 125 ml h^{-1}), urine output was significantly higher in the high-replacement group, and urine osmolality was significantly higher in the low-replacement group.[43] However, no differences were found between groups in 48-h fluid balance or GFR.

Intraoperative oliguria due to moderate fluid restriction is not therefore detrimental to renal outcome. Excretion of a fluid excess in the range of 1.5–2 litres may take more than 2 days in healthy volunteers and even more in surgical patients, indicating that the functional demands of the kidney may be increased for up to a week after surgery, depending on the nature and amount of fluid administered and the magnitude of surgery. However, the role of fluid excess in postoperative renal morbidity is unknown.

Urinary retention is commonly seen after surgery, and is a recognized complication of spinal and epidural local anaesthetic techniques, as well as postoperative opioid analgesia, due to their inhibitory effects on bladder muscle function.[7 101] A fluid overload may therefore increase the risk of postoperative urinary retention. However, urinary retention may occur also in the absence of overload, as in patients with prostate hypertrophy. Compared with other surgery, patients having anal or hernia surgery are at greater risk of developing postoperative urinary retention.[98] Thus, restriction of perioperative fluids in anorectal surgery reduces the risk of urinary retention.[8 16 100 120] In hernia surgery, perioperative administration of >1200 ml of fluid[103] or fluid infusions of >750 ml[46] was significantly associated with an increase in the incidence of urinary retention. In a randomized study in 133 hernia patients, administration of <500 ml fluid compared with 1300 ml, led to a lower (although non-significant) incidence of urinary retention.[61] However, a randomized study of intraoperative administration of 2 ml kg^{-1} *vs* 10 ml kg^{-1} of i.v. fluid to low-risk outpatients (no hernia or anal surgery, and no history of urinary retention in patients with regional anaesthesia),[98] found no difference in urinary retention between the groups. Retrospective studies in patients undergoing hysterectomy,[99] appendectomy,[101] and cholecystectomy,[102] did not find significant correlations between fluid administration and postoperative urinary retention.

Abdominal compartment syndrome and gastrointestinal function

The abdominal compartment syndrome (ACS) is defined as a postoperative or post-traumatic elevation in intra-abdominal pressure leading to adverse physiological effects, most commonly respiratory and renal failure.[14] Development of ACS may be associated with the administration of large amounts of fluid. Thus, the crystalloid volume administered to six patients with ACS was found to be 19 litres in <24 h.[80] Infusion of a volume equal to 15–20% of the body weight led to elevated intra-abdominal pressure and decreased respiratory function in an experimental study in pigs.[88] In addition, increased abdominal pressure has been found to stimulate ADH release, thus promoting further fluid retention.[67]

Fluid overload may lead to oedema of the gut, possibly contributing to enteric nutritional intolerance, prolonged ileus and translocation of endotoxin or bacteria, with potentially deleterious implications such as sepsis and multiorgan failure.[109 144] However, evidence from a study in 18 patients undergoing gastrointestinal surgery suggests that infusions of crystalloids as opposed to colloids may predispose them to the development of intestinal oedema.[107] These patients randomly received either lactated Ringer's solution (mean volume infused, 3850 ml), 10% hydroxyethyl starch (mean volume infused, 1358 ml), or 20% human albumin (mean volume infused, 463 ml), to maintain central venous pressure at the preoperative level. Colloid osmotic pressure was unchanged in the colloid groups, and intestinal oedema was found only in the group receiving crystalloids. Results from a study in 20 patients undergoing colonic surgery and randomized to a 'standard' postoperative fluid regimen (minimum of 3 litres of water and 154 mmol sodium day^{-1}), or a restricted postoperative fluid regimen (maximum of 2 litres of water and 77 mmol sodium day^{-1}), found a significant reduction in postoperative ileus with fluid restriction (4.0 *vs* 6.5 days).[70] Furthermore, postoperative hospital stay decreased from a median of 9–6 days in the patients with the restricted postoperative fluid regimen. Lowered concentrations of plasma proteins may follow administration of 2 litres of saline even in the absence of surgery,[71 87] and in experimental studies hypoproteinaemia was associated with decreased gastrointestinal motility.[41] In a prospective study in vascular surgery, an albumin concentration of <35 g litre^{-1} did not correlate with increased duration of postoperative ileus, compared with patients where the concentration of albumin was maintained above 35 g litre^{-1} with albumin infusions.[145] In experimentally performed gastrointestinal anastomoses in rabbits, administration of 5 ml kg^{-1} h^{-1} of isotonic saline during surgery followed by 200 ml in the first 48 h after surgery (compared with no fluid administration), led to a significant increase in tissue weight at the anastomotic site, persisting for 5 days after surgery.[17] The resulting impairment in tissue oxygenation may potentially have deleterious effects on anastomotic healing. The available data from these studies are preliminary and need to be addressed in future, randomized, large-scale clinical trials.

Oedema, wound healing and tissue hypoxaemia

Oedema is a clinical sign of subcutaneous fluid accumulation, which inevitably leads to impaired oxygen diffusion and decreased tissue oxygen tension, due to increased endothelial cellular distance. The relation between serum colloid osmotic pressure and interstitial oedema is not directly proportional, since the oedema becomes progressively greater as serum colloid pressure decreases.[73] Tissue oxygen tension in experimental wounds, measured by aspiration of fluid from an implanted mesh cylinder, was progressively lowered with increasing amounts of fluid administered, when 2.5, 5 or 10 ml kg^{-1} of isotonic saline solution was administered to rabbits.[44] Furthermore, when 10 ml kg^{-1} of isotone saline was administered, it took 3.5 days for tissue oxygen tension to recover to control values. In a randomized study in 42 patients scheduled for major abdominal surgery, 24 h of intra- and postoperative administration of 3 litres of hydroxyethyl starch and 3 litres of Ringer's solution was compared with 11.7 litres of Ringer's solution. There was a resulting significant decrease in tissue oxygen tension (measured via a catheter inserted in the deltoid muscle) in the crystalloid group.[66] However, in a randomized trial in major abdominal surgery, replacement of fluid according to measurements of subcutaneous oxygen tension (via a silicone catheter inserted subcutaneously in the upper arm) rather than by clinical criteria (5.7 *vs* 4.6 litres of crystalloid administered on the day of surgery), resulted in improved collagen accumulation in wounds.[42] Since wound healing may be inhibited by tissue hypoxaemia,[51] the risk of decreased oxygen tension secondary to interstitial fluid accumulation should be further evaluated in studies of low *vs* high fluid administration.

Coagulation

Impaired coagulation is a recognized complication of the use of synthetic colloids for volume replacement.[38] In contrast, infusions of crystalloids have been demonstrated to induce a hypercoagulable state both *in vitro* and *in vivo*,[114 115] which is not seen with some colloid infusions.[56] The mechanisms behind the hypercoagulable effects of crystalloids are unknown, but decreased activity of anticoagulatory factors may be of importance.[116] These findings have been confirmed in 60 patients undergoing major abdominal surgery, randomized to receive i.v fluids during or after the operation (i.v. Hartmann's solution 1 litre h^{-1} of operation and dextrose-saline 2–3 litres 24 h^{-1} for 2 days), or receiving no i.v. fluids during or after surgery.[50] The incidence of postoperative deep venous thrombosis was significantly higher in the patients receiving fluids (30%), compared with only 7% in the patients who did not receive i.v. fluid. Furthermore, the patients receiving fluids became significantly more haemodilute and hypercoagulable compared with those who did not. However, the results from this study are difficult to interpret, since administration of no intraoperative fluids in abdominal surgery is not compatible with common practice.

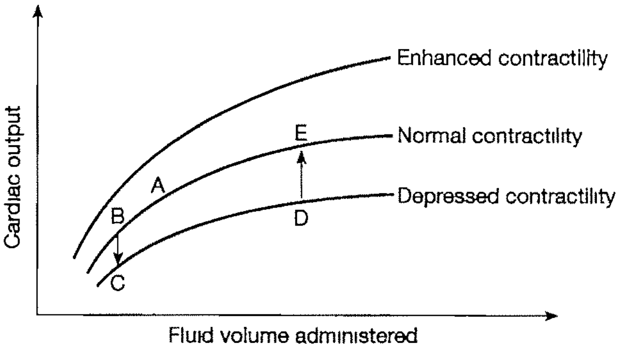


Fig 2 Relationship between cardiac output and fluid administration General anaesthesia or extensive epidural/spinal anaesthesia result in venodilatation and cardiac depression Venodilatation leads to a reduction in preload depicted by transfer from Point A (baseline) to B on the normal contractility curve Cardiac depression results in a fall to a depressed contractility curve (Point C) Restoration of cardiac output with fluid alone is depicted by the line from Point C to D With resolution of epidural anaesthesia or emergence from general anaesthesia, the patient is apt to be hyperdynamic and fluid overloaded (Point E) By contrast, if extensive epidural/spinal anaesthesia is managed with vasopressors, restoration of contractility (Point C to B) and venous tone (Point B to A) can be achieved without fluid loading

Specific considerations

Regional anaesthesia

In theory, regional anaesthesia should be followed by decreased requirements for intraoperative fluid administration due to a decrease in perioperative blood loss.[57 111] In a retrospective study of mortality during a 10-yr period of hip and knee replacement surgery, mortality decreased from 0.4 to 0.1% concomitant with extensive changes in anaesthetic technique, including a shift from general to epidural anaesthesia.[121] In addition, intraoperative fluid administration was reduced from 3108 to 1563 ml during that 10-yr period. Although cardiac output may be increased by increasing preload (Fig. 2), it may also be increased by administering sympathomimetics, leading to improved myocardial contractility with unchanged preload. Regional anaesthesia to the upper thoracic dermatomes is associated with a significant reduction in preload and an impairment of cardiac sympathetic drive, resulting in a reduction in cardiac output and hypotension.[123] A substantial volume of fluid is required to augment cardiac output in this setting,[148] whereas vasopressors with α and β activity, such as ephedrine,[122] dopamine[72] or epinephrine, can restore cardiac output without excessive volume administration. Low levels of spinal or epidural anaesthesia (T8 or below) usually result in minimal circulatory changes, as the compensatory vasoconstriction in the upper part of the body is sufficient to offset the dilatation in the lower extremities.[69] In this setting, excessive fluid is usually not needed to preserve haemodynamic stability. Thus, fluid administration prior to spinal or epidural anaesthesia, in an attempt to prevent hypotension; is a common cause of fluid overload in otherwise healthy patients (Fig. 2), and may amount to several litres of fluid administered prior to surgery.[105] Several randomized clinical trials of preload *vs* no preload in women undergoing Caesarean section,[49 113] and elderly patients with hip fractures,[13] have found that a preload produces a marginal, if any, reduction in the incidence of hypotension. The lack of effect may be attributed to several factors, such as only a transient volume expansion from the infused fluids, or increased secretion of ANP.[105] Whatever the type of infused solution, rapid i.v. administration causes a significant increase in central venous pressure,[55] pulmonary wedge pressure[78] and haemodilution,[136] with possible detrimental consequences from increased lung water content.[75] A more rational approach may therefore be the use of vasopressors instead of a high-volume preload during regional anaesthesia. A randomized study comparing an ephedrine infusion with a 15 ml kg^{-1} crystalloid infusion in 54 patients undergoing elective gynaecological surgery with spinal anaesthesia, reported a significantly lower incidence of hypotension with the ephedrine infusion (22 *vs* 55%).[34]

Immobilization

Prolonged bed rest, which commonly occurs after major surgery, leads to a decrease in plasma volume of 300–500 ml, as well as a decrease in blood volume with negative sodium balance and loss of total body water.[18 82 83] These changes occur within the first few days of bed rest. Concomitantly, the extracellular volume has been found to be relatively increased compared with the intravascular volume during 1–2 weeks of bed rest.[37 81] The effect of bed rest on the hormones influencing fluid balance is debatable since either a small increase,[81] or no change,[18] in aldosterone and renin activity has been observed. Bed rest *per se* has been demonstrated to lead to a decrease in muscle potassium and intracellular water (intracellular dehydration) after 4 days of immobilization in healthy volunteers.[9] Exercise may improve renal osmolar clearance in healthy volunteers.[32] In another study in healthy volunteers, physical exercise after 7 days of bed rest had only negligible effects on fluid and ion balance compared with no exercise.[150] Further data from healthy volunteers indicate that mild exercise may increase urine flow and GFR above levels found at rest, and that only more severe exercise inhibits renal function, probably due to increased secretion of aldosterone and ADH, and a reduced GFR.[53]

The effects of immobilization on fluid balance *per se* have not been investigated in surgical patients, and whether fluid excretion is promoted by postoperative mobilization remains to be clarified. These issues may have important clinical implications due to the adverse effects on organ function of an inappropriate fluid overload. In contrast, an adequate intravascular volume is a prerequisite for mobilization. However, it may be hypothesized that a perioperative fluid excess may hinder postoperative mobilization due to the resulting increased cardiopulmonary demands of exercise.

Conclusions

So far, no widely accepted recommendations are available for the optimal perioperative fluid regimen. A large variability in fluid regimen has been noted throughout the surgical specialties. Except for the relatively 'dry' regimen that have been advocated in pulmonary surgery,[52 84 149] it has been common practice to administer relatively large amounts of fluid (regardless of blood loss or anaesthetic technique).[19 22 35 36 66 134] Preoperative dehydration from preoperative fasting (often for >12 h), bowel preparation or underlying illness certainly needs to be corrected.

On the other hand, perioperative administration of *large* amounts of crystalloids seems to have significant side-effects in several organ systems including the heart, primarily due to the potential impairment of left ventricular stroke volume, and the possibility of developing myocardial ischaemia. Pulmonary function may be impaired by accumulation of interstitial fluid, which may contribute to the development of pulmonary oedema, atelectasis, pneumonia or respiratory failure.[19] The resulting decreased tissue oxygenation may lead to impaired wound healing. Paralytic ileus may be prolonged by excess perioperative fluid administration.[70] Finally, excess fluid administration accentuates the water- and sodium-conserving effects of the surgical stress response, and may increase the risk of electrolyte disturbances such as hyponatraemia and metabolic acidosis.[20 118]

In contrast, the widespread use of 'dry' fluid regimen in pulmonary surgery with resulting decrease in pulmonary morbidity supports the safety of low-volume fluid regimen in high-risk patients undergoing major surgical procedures.

Achievement of optimal fluid status is not just a matter of fluid substitution *per se* but is also related to the pathophysiology of the surgery. To clarify the implications of perioperative fluid excess, randomized, prospective clinical studies are needed where 'high' *vs* 'low' fluid regimen are undertaken in well-defined surgical procedures. Outcome assessments from studies of various organ dysfunctions and the associated morbidity are necessary to provide rational recommendations for perioperative fluid administration.

Acknowledgement

This work was supported by a grant from the Danish Research Council (number 22-01-0160).

References

1 Alpert RA, Roizen MF, Hamilton WK, *et al* Intraoperative urinary output does not predict postoperative renal function in patients undergoing abdominal aortic revascularization. *Surgery* 1984; **95**: 707–11

2 Andersen LJ, Jensen TU, Bestle MH, Bie P Isotonic and hypertonic sodium loading in supine humans. *Acta Physiol Scand* 1999; **166**: 23–30

3 Andersen LJ, Jensen TU, Bestle MH, Bie P Gastrointestinal osmoreceptors and renal sodium excretion in humans. *Am J Physiol Regul Integr Comp Physiol* 2000, **278**. R287–94

4 Andersen LJ, Norsk P, Johansen LB, Christensen P, Engstrom T, Bie P. Osmoregulatory control of renal sodium excretion after sodium loading in humans *Am J Physiol* 1998; **275**: R1833–42

5 Arieff AI. Fatal postoperative pulmonary edema: pathogenesis and literature review. *Chest* 1999; **115**: 1371–7

6 Artz Clinical observations on the use of dextran and modified fluid gelatin in combat casualties. *Surgery* 1955; **37**: 612–21

7 Axelsson K, Mollefors K, Olsson JO, Lingardh G, Widman B. Bladder function in spinal anaesthesia. *Acta Anaesthesiol Scand* 1985; **29**: 315–21

8 Bailey HR, Ferguson JA. Prevention of urinary retention by fluid restriction following anorectal operations. *Dis Colon Rectum* 1976; **19**: 250–2

9 Bergstrom JP, Larsson J, Nordstrom H, *et al.* Influence of injury and nutrition on muscle water and electrolytes: effect of severe injury, burns and sepsis. *Acta Chir Scand* 1987; **153**: 261–6

10 Bessey PQ, Lowe KA. Early hormonal changes affect the catabolic response to trauma. *Ann Surg* 1993; **218**: 476–89

11 Bessey PQ, Watters JM, Aoki TT, Wilmore DW. Combined hormonal infusion simulates the metabolic response to injury. *Ann Surg* 1984; **200**: 264–81

12 Bonnet F, Harari A, Thibonnier M, Viars P. Suppression of antidiuretic hormone hypersecretion during surgery by extradural anaesthesia. *Br J Anaesth* 1982; **54**: 29–36

13 Buggy D, Higgins P, Moran C, O'Brien D, O'Donovan F, McCarroll M. Prevention of spinal anesthesia-induced hypotension in the elderly: comparison between preanesthetic administration of crystalloids, colloids, and no prehydration. *Anesth Analg* 1997; **84**: 106–10

14 Burch JM, Moore EE, Moore FA, Franciose R. The abdominal compartment syndrome *Surg Clin North Am* 1996; **76**: 833–42

15 Bush HL, LoGerfo FW, Weisel RD, Mannick JA, Hechtman HB. Assessment of myocardial performance and optimal volume loading during elective abdominal aortic aneurysm resection. *Arch Surg* 1977, **112**. 1301–5

16 Campbell ED. Prevention of urinary retention after anorectal operations *Dis Colon Rectum* 1972; **15**: 69–70

17 Chan ST, Kapadia CR, Johnson AW, Radcliffe AG, Dudley HA. Extracellular fluid volume expansion and third space sequestration at the site of small bowel anastomoses. *Br J Surg* 1983; **70**: 36–9

18 Chobanian AV, Lille RD, Tercyak A, Blevins P. The metabolic and hemodynamic effects of prolonged bed rest in normal subjects *Circulation* 1974, **49**: 551–9

19 Christopherson R, Beattie C, Frank SM, et *al.* Perioperative morbidity in patients randomized to epidural or general anesthesia for lower extremity vascular surgery *Anesthesiology* 1993; **79**: 422–34

20 Chung HM, Kluge R, Schrier RW, Anderson RJ. Postoperative hyponatremia. A prospective study. *Arch Intern Med* 1986, **146** 333–6

21 Cleland J, Pluth JR, Tauxe WN, Kirklin JW. Blood volume and body fluid compartment changes soon after closed and open intracardiac surgery. *J Thorac Cardiovasc Surg* 1966, **52**: 698–705

22 Cohn LH, Powell MR, Seidlitz L, Hamilton WK, Wylie EJ. Fluid requirements and shifts after reconstruction of the aorta. *Am J Surg* 1970; **120**: 182–6

23 Collins JV, Cochrane GM, Davis J, Benatar SR, Clark TJ. Some aspects of pulmonary function after rapid saline infusion in healthy subjects. *Clin Sci Mol Med* 1973; **45**: 407–10

24 Deleted

25 Cousins MJ, Mazze RI. Anaesthesia, surgery and renal function: immediate and delayed effects *Anaesth Intensive Care* 1973; **1**: 355–73

26 Cousins MJ, Skowronski G, Plummer JL Anaesthesia and the kidney *Anaesth Intensive Care* 1983; **11**: 292–320

27 Desborough JP. The stress response to trauma and surgery. *Br J Anaesth* 2000; **85**: 109–17

28 Drummer C, Fiedler F, Konig A, Gerzer R. Urodilatin, a kidney-derived natriuretic factor, is excreted with a circadian rhythm and is stimulated by saline infusion in man. *J Am Soc Nephrol* 1991, **1**: 1109–13

29 Drummer C, Gerzer R, Heer M, *et al.* Effects of an acute saline infusion on fluid and electrolyte metabolism in humans. *Am J Physiol* 1992; **262** F744–54

30 Drummer C, Heer M, Baisch F, *et al.* Diuresis and natriuresis following isotonic saline infusion in healthy young volunteers before, during, and after HDT. *Acta Physiol Scand Suppl* 1992; **604**: 101–11

31 Finn PJ, Plank LD, Clark MA, Connolly AB, Hill GL Progressive cellular dehydration and proteolysis in critically ill patients *Lancet* 1996; **347**: 654–6

32 Fuller JH, Bernauer EM, Adams WC. Renal function, water and electrolyte exchange during bed rest with daily exercise *Aerosp Med* 1970; **41**: 60–72

33 Deleted

34 Gajraj NM, Victory RA, Pace NA, Van Elstraete AC, Wallace DH. Comparison of an ephedrine infusion with crystalloid administration for prevention of hypotension during spinal anesthesia. *Anesth Analg* 1993; **76**: 1023–6

35 Garnett RL, MacIntyre A, Lindsay P, *et al.* Perioperative ischaemia in aortic surgery: combined epidural/general anaesthesia and epidural analgesia *vs* general anaesthesia and i.v. analgesia *Can J Anaesth* 1996; **43**: 769–77

36 Glaser F, Sannwald GA, Buhr HJ, *et al.* General stress response to conventional and laparoscopic cholecystectomy *Ann Surg* 1995; **221**: 372–80

37 Greenleaf JE, Bernauer EM, Young HL, *et al.* Fluid and electrolyte shifts during bed rest with isometric and isotonic exercise. *J Appl Physiol* 1977; **42**: 59–66

38 Grocott MPW, Mythen MG. Fluid therapy. *Baillière's Clin Anaesthesiol* 1999; **13**: 363–81

39 Gump FE, Kinney JM, Iles M, Long CC. Duration and significance of large fluid loads administered for circulatory support. *J Trauma* 1970; **10**: 431–9

40 Gutelius JR, Shizgal HM, Lopez G. The effect of trauma on extracellular water volume. *Arch Surg* 1968, **97**: 206–14

41 Harden RP, Thompson WD, Ravdin IS, Frank IL. The influence of the serum protein on the motility of the small intestine. *Surg Gynecol Obstet* 2001; **66**: 819–21

42 Hartmann M, Jonsson K, Zederfeldt B. Effect of tissue perfusion and oxygenation on accumulation of collagen in healing wounds Randomized study in patients after major abdominal operations. *Eur J Surg* 1992; **158**: 521–6

43 Hatch DA, Barry JM, Norman DJ. A randomized study of intravenous fluid replacement following living-donor renal transplantation. *Transplantation* 1985; **40**: 648–51

44 Heughan C, Niinikoski J, Hunt TK. Effect of excessive infusion of saline solution on tissue oxygen transport. *Surg Gynecol Obstet* 1972; **135**. 257–60

45 Hillebrecht A, Schulz H, Meyer M, Baisch F, Beck L, Blomqvist CG. Pulmonary responses to lower body negative pressure and fluid loading during head-down tilt bedrest. *Acta Physiol Scand Suppl* 1992; **604**: 35–42

46 Hirano T, Yoshioka H. Post-operative urinary retention after inguinal herniorrhaphy with spinal anaesthesia. *Med Sci Res* 1993; **21**: 693–4

47 Hutchin P, Terzi RG, Hollandsworth LC. Renal response to intraoperative fluid administration. *Surg Gynecol Obstet* 1969; **129**: 795–8

48 Ishihara H, Ishida K, Oyama T, Kudo T, Kudo M. Effects of general anaesthesia and surgery on renal function and plasma ADH levels. *Can Anaesth Soc J* 1978; **25**: 312–8

49 Jackson R, Reid JA, Thorburn J. Volume preloading is not essential to prevent spinal-induced hypotension at Caesarean section. *Br J Anaesth* 1995; **75**: 262–5

50 Janvrin SB, Davies G, Greenhalgh RM. Postoperative deep vein thrombosis caused by intravenous fluids during surgery. *Br J Surg* 1980; **67**: 690–3

51 Jonsson K, Jensen JA, Goodson WH, *et al.* Tissue oxygenation, anemia, and perfusion in relation to wound healing in surgical patients. *Ann Surg* 1991; **214**: 605–13

52 Jordan S, Mitchell JA, Quinlan GJ, Goldstraw P, Evans TW. The pathogenesis of lung injury following pulmonary resection. *Eur Respir J* 2000; **15**: 790–9

53 Kachadorian WA, Johnson RE. Renal responses to various rates of exercise. *J Appl Physiol* 1970, **28**: 748–52

54 Kamp-Jensen M, Olesen KL, Bach V, Schutten HJ, Engquist A. Changes in serum electrolyte and atrial natriuretic peptide concentrations, acid–base and haemodynamic status after rapid infusion of isotonic saline and Ringer lactate solution in healthy volunteers. *Br J Anaesth* 1990; **64**: 606–10

55 Karinen J, Rasanen J, Alahuhta S, Jouppila R, Jouppila P. Effect of crystalloid and colloid preloading on uteroplacental and maternal haemodynamic state during spinal anaesthesia for Caesarean section. *Br J Anaesth* 1995; **75**: 531–5

56 Karoutsos S, Nathan N, Lahrimi A, Grouille D, Feiss P, Cox DJ. Thrombelastogram reveals hypercoagulability after administration of gelatin solution. *Br J Anaesth* 1999; **82**: 175–7

57 Kehlet H. Modification of responses to surgery by neural blockade: clinical implications In: Cousins MJ, Bridenbaugh PO, eds. *Neural Blockade in Clinical Anesthesia and Management of Pain*, 3rd Edn. Philadelphia: Lippincott-Raven, 1998; 129–75

58 Kehlet H. Surgical stress response: does endoscopic surgery confer an advantage? *World J Surg* 1999; **23**: 801–7

59 Kidd JE, Gilchrist NL, Utley RJ, Nicholls MG, Espiner EA, Yandle TG. Effect of opiate, general anaesthesia and surgery on plasma atrial natriuretic peptide levels in man. *Clin Exp Pharmacol Physiol* 1987; **14**: 755–60

60 Kongstad L, Moller AD, Grande PO. Reflection coefficient for albumin and capillary fluid permeability in cat calf muscle after traumatic injury. *Acta Physiol Scand* 1999; **165**: 369–77

61 Kozol RA, Mason K, McGee K. Post-herniorrhaphy urinary retention: a randomized prospective study. *J Surg Res* 1992; **52**: 111–2

62 Kudoh A, Ishihara H, Matsuki A. Renin-aldosterone system and atrial natriuretic peptide during anesthesia in orthopedic patients over 80 years of age. *J Clin Anesth* 1999; **11**: 101–7

63 Kudoh A, Sakai T, Ishihara H, Matsuki A. Renin-aldosterone in elderly patients with hyperkalaemia under anaesthesia. *Eur J Anaesthesiol* 1999; **16**: 231–5

64 Ladegaard-Pedersen HJ. Postoperative changes in blood volume and colloid osmotic pressure. *Acta Chir Scand* 1969; **135**: 94–104

65 Ladegaard-Pedersen HJ, Engell HC. A comparison between the changes in the distribution volumes of inulin and [51Cr]EDTA after major surgery. *Scand J Clin Lab Invest* 1975; **35**: 109–13

66 Lang K, Boldt J, Suttner S, Haisch G. Colloids *versus* crystalloids and tissue oxygen tension in patients undergoing major abdominal surgery. *Anesth Analg* 2001; **93**: 405–9

67 Le Roith D, Bark H, Nyska M, Glick SM. The effect of abdominal pressure on plasma antidiuretic hormone levels in the dog. *J Surg Res* 1982; **32**: 65–9

68 Lewis H, Wilkins M, Selwyn B, Yelland U, Griffith M, Bhoola KD. Relationship between ANP, cyclic GMP and tissue kallikrein following saline infusion in healthy volunteers. *Adv Exp Med Biol* 1989; **247A**: 281–6

69 Liu SS, McDonald SB. Current issues in spinal anesthesia. *Anesthesiology* 2001; **94**: 888–906

70 Lobo DN, Bostock KA, Neal KR, Perkins AC, Rowlands BJ, Allison SP. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomised control trial. *Lancet* 2002; **359**: 1812–18

71 Lobo DN, Stanga Z, Simpson JA, Anderson JA, Rowlands BJ, Allison SP. Dilution and redistribution effects of rapid 2-litre infusions of 0.9% (w/v) saline and 5% (w/v) dextrose on haematological parameters and serum biochemistry in normal subjects: a double-blind crossover study. *Clin Sci (Lond)* 2001; **101**: 173–9

72 Lundberg J, Lundberg D, Norgren L, Werner O. Dopamine counteracts hypertension during general anesthesia and hypotension during combined thoracic epidural anesthesia for abdominal aortic surgery. *J Cardiothorac Anesth* 1990; **4**: 348–53

73 Lundsgaard-Hansen P, Pappova E. Colloids *versus* crystalloids as volume substitutes: clinical relevance of the serum oncotic pressure *Ann Clin Res* 1981; **13** (Suppl 33): 5–17

74 Lundvall J, Lanne T. Large capacity in man for effective plasma volume control in hypovolaemia via fluid transfer from tissue to blood. *Acta Physiol Scand* 1989, **137**: 513–20

75 MacLennan FM, MacDonald AF, Campbell DM. Lung water during the puerperium. *Anaesthesia* 1987; **42**: 141–7

76 Mangano DT, Van Dyke DC, Ellis RJ. The effect of increasing preload on ventricular output and ejection in man. Limitations of the Frank–Starling Mechanism. *Circulation* 1980; **62**: 535–41

77 Manny J, Grindlinger GA, Dennis RC, Weisel RD, Hechtman HB.

Myocardial performance curves as guide to volume therapy. *Surg Gynecol Obstet* 1979; **149**: 863–73

78 Marhofer P, Faryniak B, Oismuller C, Koinig H, Kapral S, Mayer N. Cardiovascular effects of 6% hetastarch and lactated Ringer's solution during spinal anesthesia. *Reg Anesth Pain Med* 1999; **24**: 399–404

79 Matthay MA, Fukuda N, Frank J, Kallet R, Daniel B, Sakuma T. Alveolar epithelial barrier. Role in lung fluid balance in clinical lung injury. *Clin Chest Med* 2000; **21**. 477–90

80 Maxwell RA, Fabian TC, Croce MA, Davis KA. Secondary abdominal compartment syndrome: an underappreciated manifestation of severe hemorrhagic shock. *J Trauma* 1999; **47**: 995–9

81 Melada GA, Goldman RH, Luetscher JA, Zager PG. Hemodynamics, renal function, plasma renin, and aldosterone in man after 5 to 14 days of bedrest. *Aviat Space Environ Med* 1975; **46**: 1049–55

82 Miller PB, Johnson RL, Lamb LE. Effects of four weeks of absolute bed rest on circulatory functions in man. *Aerosp Med* 1964; **35**. 1194–2000

83 Miller PB, Johnson RL, Lamb LE. Effects of moderate physical exercise during four weeks of bed rest on circulatory functions in man. *Aerosp Med* 1965; **35**: 1077–82

84 Mitchell JP, Schuller D, Calandrino FS, Schuster DP. Improved outcome based on fluid management in critically ill patients requiring pulmonary artery catheterization. *Am Rev Respir Dis* 1992; **145**: 990–8

85 Moore FD. *Metabolic Care of the Surgical Patient*. Philadelphia: WB Saunders Co., 1959

86 Moore FD, Shires G. Moderation. *Ann Surg* 1967; **166**: 300–1

87 Mullins RJ, Garrison RN. Fractional change in blood volume following normal saline infusion in high-risk patients before noncardiac surgery. *Ann Surg* 1989; **209**: 651–9

88 Mutoh T, Lamm WJ, Embree LJ, Hildebrandt J, Albert RK. Volume infusion produces abdominal distension, lung compression, and chest wall stiffening in pigs. *J Appl Physiol* 1992; **72**: 575–82

89 Mythen MG, Webb AR. Perioperative plasma volume expansion reduces the incidence of gut mucosal hypoperfusion during cardiac surgery. *Arch Surg* 1995; **130**: 423–9

90 Needleman P, Greenwald JE. Atriopeptin: a cardiac hormone intimately involved in fluid, electrolyte, and blood-pressure homeostasis. *N Engl J Med* 1986; **314**: 828–34

91 Nielsen OM, Engell HC. Extracellular fluid volume and distribution in relation to changes in plasma colloid osmotic pressure after major surgery. A randomized study. *Acta Chir Scand* 1985; **151**: 221–5

92 Nielsen OM, Engell HC. Increased glomerular filtration rate in patients after reconstructive surgery on the abdominal aorta. *Br J Surg* 1986; **73**: 34–7

93 Nielsen OM, Engell HC. The importance of plasma colloid osmotic pressure for interstitial fluid volume and fluid balance after elective abdominal vascular surgery. *Ann Surg* 1986; **203**: 25–9

94 Norsk P, Drummer C, Rocker L, *et al.* Renal and endocrine responses in humans to isotonic saline infusion during microgravity. *J Appl Physiol* 1995, **78**: 2253–9

95 Parquin F, Marchal M, Mehiri S, Herve P, Lescot B. Post-pneumonectomy pulmonary edema: analysis and risk factors. *Eur J Cardiothorac Surg* 1996, **10**. 929–32

96 Parving HH, Rossing N, Nielsen SL, Lassen NA. Increased transcapillary escape rate of albumin, IgG, and IgM after plasma volume expansion. *Am J Physiol* 1974; **227**. 245–50

97 Patel RL, Townsend ER, Fountain SW. Elective pneumonectomy: factors associated with morbidity and operative mortality. *Ann Thorac Surg* 1992, **54**: 84–8

98 Pavlin DJ, Pavlin EG, Fitzgibbon DR, Koerschgen ME, Plitt TM. Management of bladder function after outpatient surgery. *Anesthesiology* 1999; **91**: 42–50

99 Petros JG, Alameddine F, Testa E, Rimm EB, Robillard RJ. Patient-controlled analgesia and postoperative urinary retention after hysterectomy for benign disease. *J Am Coll Surg* 1994, **179**. 663–7

100 Petros JG, Bradley TM. Factors influencing postoperative urinary retention in patients undergoing surgery for benign anorectal disease. *Am J Surg* 1990, **159**. 374–6

101 Petros JG, Mallen JK, Howe K, Rimm EB, Robillard RJ. Patient-controlled analgesia and postoperative urinary retention after open appendectomy. *Surg Gynecol Obstet* 1993, **177**. 172–5

102 Petros JG, Rimm EB, Robillard RJ. Factors influencing urinary tract retention after elective open cholecystectomy. *Surg Gynecol Obstet* 1992; **174**: 497–500

103 Petros JG, Rimm EB, Robillard RJ, Argy O. Factors influencing postoperative urinary retention in patients undergoing elective inguinal herniorrhaphy. *Am J Surg* 1991; **161**. 431–3

104 Polanczyk CA, Rohde LE, Goldman L, *et al.* Right heart catheterization and cardiac complications in patients undergoing noncardiac surgery: an observational study. *JAMA* 2001; **286**: 309–14

105 Pouta AM, Karinen J, Vuolteenaho OJ, Laatikainen TJ. Effect of intravenous fluid preload on vasoactive peptide secretion during Caesarean section under spinal anaesthesia. *Anaesthesia* 1996; **51**: 128–32

106 Priano LL, Smith JD, Cohen JI, Everts EE. Intravenous fluid administration and urine output during radical neck surgery. *Head Neck* 1993; **15**: 208–15

107 Prien T, Backhaus N, Pelster F, Pircher W, Bunte H, Lawin P. Effect of intraoperative fluid administration and colloid osmotic pressure on the formation of intestinal edema during gastrointestinal surgery. *J Clin Anesth* 1990; **2**: 317–23

108 Pull ter Gunne AJ, Bruining HA, Obertop H. Haemodynamics and 'optimal' hydration in aortic cross clamping. *Neth J Surg* 1990; **42**: 113–7

109 Ratner LE, Smith GW. Intraoperative fluid management. *Surg Clin North Am* 1993; **73**: 229–41

110 Roberts JP, Roberts JD, Skinner C, Shires GT, Illner H, Canizzaro PC. Extracellular fluid deficit following operation and its correction with Ringer's lactate. A reassessment. *Ann Surg* 1985; **202**: 1–8

111 Rodgers A, Walker N, Schug S, *et al.* Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. *Br Med J* 2000, **321**. 1493–7

112 Roth E, Lax LC, Maloney JV. Ringer's lactate solution and extracellular fluid volume in the surgical patient: a critical analysis. *Ann Surg* 1969, **169**: 149–64

113 Rout CC, Rocke DA, Levin J, Gouws E, Reddy D. A reevaluation of the role of crystalloid preload in the prevention of hypotension associated with spinal anesthesia for elective Cesarean section. *Anesthesiology* 1993; **79**: 262–9

114 Ruttmann TG, James MF, Aronson I. *In vivo* investigation into the effects of haemodilution with hydroxyethyl starch (200/0.5) and normal saline on coagulation. *Br J Anaesth* 1998; **80**. 612–6

115 Ruttmann TG, James MF, Viljoen JF. Haemodilution induces a hypercoagulable state. *Br J Anaesth* 1996; **76**: 412–4

116 Ruttmann TG, Jamest MF, Lombard EH. Haemodilution-induced enhancement of coagulation is attenuated in vitro by restoring antithrombin III to pre-dilution concentrations. *Anaesth Intensive Care* 2001; **29**: 489–93

117 Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocr Rev* 2000; **21**: 55–89

118 Scheingraber S, Rehm M, Sehmisch C, Finsterer U. Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. *Anesthesiology* 1999; **90**: 1265–70

119 Schutten HJ, Johannessen AC, Torp-Pedersen C, Sander-Jensen K, Bie P, Warberg J. Central venous pressure—a physiological stimulus for secretion of atrial natriuretic peptide in humans? *Acta Physiol Scand* 1987; **131**: 265–72

120 Scoma JA Catheterization in anorectal surgery. *Arch Surg* 1975; **110**: 1506

121 Sharrock NE, Cazan MG, Hargett MJ, Williams-Russo P, Wilson PDJ. Changes in mortality after total hip and knee arthroplasty over a ten-year period. *Anesth Analg* 1995; **80**: 242–8

122 Sharrock NE, Mather LE, Go G, Sculco TP. Arterial and pulmonary arterial concentrations of the enantiomers of bupivacaine after epidural injection in elderly patients. *Anesth Analg* 1998; **86**. 812–7

123 Sharrock NE, Mineo R, Urquhart B. Hemodynamic response to low-dose epinephrine infusion during hypotensive epidural anesthesia for total hip replacement. *Reg Anesth* 1990; **15**: 295–9

124 Sharrock NE, Mineo R, Urquhart B Haemodynamic effects and outcome analysis of hypotensive extradural anaesthesia in controlled hypertensive patients undergoing total hip arthroplasty. *Br J Anaesth* 1991; **67**: 17–25

125 Shippy CR, Shoemaker WC. Hemodynamic and colloid osmotic pressure alterations in the surgical patient. *Crit Care Med* 1983; **11**: 191–5

126 Shires GT, Barber A. Fluid and electrolyte management of the surgical patient. In: Schwartz RW, Shires GT, Daly JM, eds. *Principles of Surgery*, 6th Edn. New York: McGraw Hill, 1997; 53–75

127 Shires GT, Carrico J, Lightfoot S. Fluid therapy in hemorrhagic shock. *Arch Surg* 1964; **88**: 688–93

128 Shires GT, Jackson DE. Postoperative salt tolerance. *Arch Surg* 1962; **84**: 703–9

129 Shires T, Williams J, Brown F. Acute change in extracellular fluids associated with major surgical procedures. *Ann Surg* 1961; **154**: 803–10

130 Shoemaker WC, Appel P, Bland R. Use of physiologic monitoring to predict outcome and to assist in clinical decisions in critically ill postoperative patients. *Am J Surg* 1983; **146**: 43–50

131 Sinclair S, James S, Singer M. Intraoperative intravascular volume optimisation and length of hospital stay after repair of proximal femoral fracture: randomised controlled trial. *Br Med J* 1997; **315**: 909–12

132 Sinnatamby C, Edwards CR, Kitau, Irving MH. Antidiuretic hormone response to high and conservative fluid regimes in patients undergoing operation. *Surg Gynecol Obstet* 1974; **139**: 715–9

133 Slinger PD. Perioperative fluid management for thoracic surgery: the puzzle of postpneumonectomy pulmonary edema. *J Cardiothorac Vasc Anesth* 1995; **9**· 442–51

134 Thompson JE, Vollman RW, Austin DJ, Kartchner MM Prevention of hypotensive and renal complications of aortic surgery using balanced salt solution: thirteen-year experience with 670 cases. *Ann Surg* 1968; **167**: 767–77

135 Turnage WS, Lunn JJ. Postpneumonectomy pulmonary edema. A retrospective analysis of associated variables. *Chest* 1993; **103**: 1646–50

136 Ueyama H, He YL, Tanigami H, Mashimo T, Yoshiya I. Effects of crystalloid and colloid preload on blood volume in the parturient undergoing spinal anesthesia for elective Cesarean section. *Anesthesiology* 1999; **91**: 1571–6

137 Verheijen-Breemhaar L, Bogaard JM, van den Berg B, Hilvering C Post-pneumonectomy pulmonary edema. *Thorax* 1988; **43**. 323–6

138 Virtue RW, LeVine DS, Aikawa JK. Fluid shifts during the surgical period: RISA and S35 determinations following glucose, saline or lactate infusion *Ann Surg* 1966; **163**· 523–8

139 Waller DA, Gebitekin C, Saunders NR, Walker DR. Noncardiogenic pulmonary edema complicating lung resection. *Ann Thorac Surg* 1993; **55**: 140–3

140 Watters JM, Bessey PQ, Dinarello CA, Wolff SM, Wilmore DW. Both inflammatory and endocrine mediators stimulate host responses to sepsis. *Arch Surg* 1986; **121**: 179–90

141 Whittemore AD, Clowes AW, Hechtman HB, Mannick JA. Aortic aneurysm repair. Reduced operative mortality associated with maintenance of optimal cardiac performance. *Ann Surg* 1980, **192**: 414–21

142 Williams GH, Duhly RG. Hypertensive states: associated fluid and electrolyte disturbances. In: Narins RG, ed. *Maxwell and Kleman's Clinical Disorder of Fluid and Electrolyte Metabolism*, 5th Edn. New York: McGraw-Hill, 1994, 1619–48

143 Wilmore DW Metabolic response to severe surgical illness: overview. *World J Surg* 2000, **24**: 705–11

144 Wilmore DW, Smith RJ, O'Dwyer ST. The gut—a central organ following surgical stress. *Surgery* 2000; **104**: 917–23

145 Woods MS, Kelley H. Oncotic pressure, albumin and ileus: the effect of albumin replacement on postoperative ileus *Am Surg* 1993; **59**: 758–63

146 Yamaji T, Ishibashi M, Takaku F. Atrial natriuretic factor in human blood. *J Clin Invest* 1985; **76**: 1705–9

147 Zaloga GP, Hughes SS. Oliguria in patients with normal renal function. *Anesthesiology* 1990; **72**: 598–602

148 Zayas V, Blumenfeld J, Bading B. Adrenergic regulation of renin secretion and renal hemodynamics during deliberate hypotension in man. *Am J Physiol* 1993; **265**: F686–92

149 Zeldin RA, Normandin D, Landtwing D, Peters RM. Postpneumonectomy pulmonary edema. *J Thorac Cardiovasc Surg* 1984; **87**· 359–65

150 Zorbas YG, Andreyev VG, Popescu LB. Fluid-electrolyte metabolism and renal function in men under hypokinesia and physical exercise. *Int Urol Nephrol* 1988; **20**: 215–23

British Journal of Anaesthesia 89 (4): 633–5 (2002)

BJA

SHORT COMMUNICATIONS

Root-cause analysis of an airway filter occlusion: a way to improve the reliability of the respiratory circuit

P. Garnerin[1 2]*, E. Schiffer[1], E. Van Gessel[1] and F. Clergue[1]

[1]Anaesthesiology Division and [2]Quality of Care Unit, Geneva University Hospitals, Rue Micheli-du-Crest 24, CH-1211 Geneva 14, Switzerland

**Corresponding author*

Background. To show how root-cause analysis can identify system-level factors causing critical incidents and accidents, we present an investigation of the occlusion of an airway filter during anaesthesia.

Method. The investigation was based on a framework specifically developed for the analysis of medical accidents. This framework helped to identify the chronology and outcome of the case, the care management problems and the factors that led to the event. Information was obtained by interviewing the anaesthesiologist in charge of the patient.

Results. Occlusion was not recognized because the filter was hidden under the drapes and below the patient's head. To reduce the frequency of this event, we recommend that filters should be visible, placed above the level of the patient's body, or mounted on the expiratory circuit, at a distance from patient's airway.

Conclusions. To allow appropriate corrective actions, critical incidents and accidents should be systematically investigated using root-cause analysis.

Br J Anaesth 2002; **89**: 633–5

Keywords: audit, root cause analysis; ventilation, respiratory circuit; risk

Accepted for publication: May 30, 2002

Root-cause analysis is a structured and systematic approach used to identify key system-level factors that contribute to the occurrence of critical incidents and accidents. Even though this approach has proved instrumental in understanding major industrial breakdowns, root-cause analysis is seldom used in medicine to study clinical adverse events.

To illustrate the potential of such an approach, we describe the root-cause analysis of a case of filter occlusion by water and secretions during anaesthesia that could have been fatal.

Methods and results

Critical incidents and accidents are caused by a combination of equipment, active and latent failures Active failures are errors or violations committed by operators directly involved in the provision of care (e.g. administration of the wrong drug). Latent failures or root causes depend on decisions made at the upper echelons of an organization and correspond to system problems (e.g. vials look alike).[1]

To identify the root cause of the event, we used a framework developed for the investigation of medical accidents.[2] We first established the chronology and the outcome of the case. We then identified care management problems, which were defined as either equipment failures or active failures represented by deviations beyond safe limits. Finally, we listed and categorized the different factors that facilitated the occurrence of these problems. A contributory factor was considered specific when it was related to chance and general when it was a permanent feature of the system and as such represented a root cause of the incident. Information was obtained by interviewing the anaesthesiologist in charge of the case.

To devise corrective actions, we relied on two principles that are commonly combined when managing risks, namely prevention and absorption.[3] Prevention aims at removing the root causes which increase the opportunity of equipment

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Table 1 Synoptic summary of the critical incident. S=specific; G=general

Care management problem No. 1: **Airway filter occlusion**	S	G
Clinical context and patient factors		
High volume of secretions		
Contributory factors		
Organizational and management factors		
None		
Work environment factors		
Airway filter with hydrophobic membrane		X
Team factors		
None		
Individual factors		
None		
Task factors		
Airway filter routinely positioned bellow the patient's head during facial surgery		X
Care management problem No. 2: **Delayed identification of airway filter occlusion**	**S**	**G**
Clinical context and patient factors		
Secretion in the patient's airway		
Contributory factors		
Organizational and management factors		
Lack of specific warning about the risk of occlusion associated with airway filters including a hydrophobic membrane, during training		X
Work environment factors		
None		
Team factors		
None		
Individual factors		
Unfamiliarity of the junior anaesthesiologist with occlusion of airway filters including a hydrophobic membrane	X	
Task factors		
Airway filter routinely positioned under the drapes during facial surgery		X

or active failures whereas absorption is intended at eliminating root causes that hinder the early identification and correction of active failures.

Chronology and outcome

A 13-yr-old boy with maxillo-facial Cacrum Oris (Noma) was to have elective plastic reconstruction. Patient history, examination, and laboratory findings were otherwise normal.

During surgery, the respiratory system consisted of a ventilator connected via a breathing tubing to an airway pressure and gas analyser and a Y-piece, fitted to a BB 25 airway filter (Pall Medical, Ann Arbor, MI, USA). The filter was connected to a catheter mount tubing connector and a tracheal tube. The ventilator was checked before surgery. To provide convenient access to the surgical site, the filter was positioned below the patient's head under the drapes.

The beginning of the procedure was uneventful but after 2 h, the peak airway pressure progressively increased, exceeding the 30 cm H_2O threshold. Both ventilator and analyser pressure alarms sounded. The junior anaesthesiologist in charge of the case immediately increased the inspired oxygen concentration. Noisy chest sounds were heard on auscultation, which decreased after large amounts of secretion were removed using a suction catheter inserted into the tracheal tube. However, the peak airway pressure remained greater than 40 cm H_2O. Four minutes after the alarms were triggered, inflation of the patient's lungs became impossible. Oxygen saturation decreased to 80%. When the junior anaesthesiologist connected a self-inflating bag directly to the tracheal tube, immediate lung ventilation was possible. The ventilator and the respiratory circuit were then replaced and the tracheal tube was reconnected using the same analyser, filter, and tubing connector. Ventilation remained impossible. Finally, occlusion of the filter by water and secretions was identified and the filter was changed. The patient recovered quickly and without sequel.

Identification of care management problems and contributory factors

In this critical incident, two care management problems occurred, namely an equipment failure (the occlusion of the airway filter), and its delayed identification. These two events, the combination of which led to severe hypoxaemia, were facilitated by a set of specific or general contributory factors presented in Table 1.

Corrective actions

To increase the ability of anaesthesiologists to detect filter occlusion, this critical incident was presented at several meetings and the problem was described in the information bulletin of our division. In addition, it was recommended that the airway filter always be visible. Finally, during training sessions on the management of airway and respiratory circuit occlusions, more emphasis was put on the risk of filter clogging.

To prevent liquids from accumulating in the filter, it was decided that the filter should be routinely placed above the lung level or, when this was not possible it should be mounted on the expiratory circuit at a distance from patient's airways.

New instructions for use of filters were printed on posters and displayed in all operating rooms.

Comment

This critical incident could be considered as the consequence of the anaesthesiologist's failure to apply basic knowledge. However, similar difficulties have been observed elsewhere. In two cases of mechanical occlusion of the respiratory circuit,[4 5] the first hypothesis made by anaesthesiologists with regard to the origin of restricted ventilation was bronchospasm. The true cause of the problem was only discovered by disconnecting the patient from the respiratory circuit and obtaining an appropriate oxygenation using a self-inflating bag.

In most cases, the problem is not the individual but the system. Our analysis shows that occlusion was possible because the filter had a hydrophobic membrane and was placed below the patient's head. The ability of the anaesthesiologists to detect airway filter occlusion was limited by the lack of information on the risk associated with the use of this device and by its position under the drapes. The identification of latent failures that are organizational root causes of accidents or critical incidents is, therefore, essential for devising appropriate corrective actions.

At first glance, our strategy, which combines prevention and absorption, could be perceived as convoluted. Compared with the prevailing approach of risk management which, as noted by Cooper,[6] 'depends almost solely on the anaesthetist's ability to react instinctively and flawlessly every time a problem arises', this method is much more efficient. Indeed, if Po is the probability of airway filter occlusion and Pr the probability of not recognizing in time the problem, $Po \times Pr$ will be the probability Pc of the critical incident. As a consequence, any x-fold decrease in both Po and Pr will have a multiplicative effect and result in a x^2-fold decrease of Pc whereas a x-fold decrease in Pr alone will only cause an equivalent decrease in Pc.

Given the usefulness of root-cause analysis with regard to patient safety, it is clear that we should systematically investigate critical incidents and accidents. However, reporting and analysis of such events on a routine basis and setting up appropriate corrective actions will require considerable cultural and organizational changes. Is there any alternative?

Acknowledgement

We are indebted to PALL (Schweiz) AG for providing the posters presenting the filter instructions for use.

References

1 Reason J. Understanding adverse events. human factors *Qual Health Care* 1995; 4. 80–9

2 Vincent CA, Taylor-Adams S, Chapman EJ, *et al. A Protocol for the Investigation and Analysis of Clinical Incidents.* London: University College London/Association of Litigation and Risk Management, 1999

3 Leape LL. Error in medicine. *JAMA* 1994; **272**. 1851–7

4 Norman PH, Daley MD, Walker JR, Fusetti S. Obstruction due to retained carbon dioxide absorber canister wrapping. *Anesth Analg* 1996; **83**. 425–6

5 Aarhus D, Soreide E, Holst-Larsen H. Mechanical obstruction in the anaesthesia delivery-system mimicking severe bronchospasm. *Anaesthesia* 1997, **52**: 992–4

6 Cooper JB, Newbower RS, Kitz RJ. An analysis of major errors and equipment failures in anesthesia management: considerations for prevention and detection. *Anesthesiology* 1984; **60**: 34–42

British Journal of Anaesthesia 87 (5) 635–7 (2002)

Saliva cyclic GMP increases during anaesthesia

T. Engelhardt*, H. F. Galley, F. M. MacLennan and N. R. Webster

Academic Unit of Anaesthesia and Intensive Care, Institute of Medical Sciences, University of Aberdeen, Aberdeen AB25 2ZD, UK

**Corresponding author*

Background. Cyclic GMP (cGMP) has been implicated in modulating the effects of general anaesthesia. Changes in cGMP in humans undergoing anaesthesia have not been reported previously.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Methods. In this pilot study we measured cGMP in the saliva of six healthy volunteers and eight patients undergoing general anaesthesia for minor gynaecological procedures. Samples were obtained using a commercially available sampling device and cGMP was determined with an enzyme immunoassay and results expressed as a cGMP per mg protein.

Results. There was no statistically significant variation in salivary cGMP either day-to-day or between time points in healthy volunteers. Analysis of variance of salivary cGMP of patients undergoing general anaesthesia showed that cGMP increased significantly intraoperatively and returned to preoperative levels after surgery (*P*=0.03).

Conclusions. This is the first time that real time *in vivo* changes in salivary cGMP levels during general anaesthesia in humans have been demonstrated and may allow an alternative technique for measuring depth of anaesthesia in the future.

Br J Anaesth 2002; **89**: 635–7

Keywords: anaesthesia, depth; anaesthesia, general; metabolism, second messengers; monitoring, depth of anaesthesia

Accepted for publication: May 25, 2002

Cyclic GMP (cGMP) is thought to play a central role in mediating the effects of anaesthesia. Nitric oxide is a potent stimulant of soluble guanylcyclase resulting in the production of cGMP, which in turn regulates a variety of cGMP-dependent kinases, ion channels, and phosphodiesterases. There is a reduction of minimum anaesthetic concentration (MAC) of volatile anaesthetic agents in rodents following acute administration of nitric oxide synthase inhibitors.[1] This has been disputed and not been reported in chronic administration and deletion of the type I (neuronal) nitric oxide synthase gene.[2 3]

cGMP is detectable in saliva, providing an easily accessible sample for measurement during anaesthesia. There are no previous data regarding variation in salivary cGMP in healthy subjects in the absence of anaesthesia, and therefore initial studies assessing any variation were required before undertaking studies in anaesthetized subjects. The aim of this study was to assess whether changes in salivary cGMP occurred during anaesthesia in humans.

Methods and results

Following local ethics approval and written informed consent we collected saliva from six healthy volunteers (25–32 yr) on 5 consecutive days at two time points (10:00 and 15:00 h) using a commercially available collection device, Orasure™ (Altrix Healthcare, Birkenhead, Merseyside, UK). We also collected saliva from eight ASA grade I or II patients (24–36 yr) undergoing minor obstetric procedures, immediately prior to induction, 10 min into the procedure and within 60 min after the operation. The anaesthetic regimen was standardized. All patients received induction of anaesthesia with propofol and maintenance with isoflurane/nitrous oxide in oxygen at 1.3 MAC via a facemask without the use of an airway. None of the patients had any form of pre-medication or received intraoperative opioids.

Saliva samples were frozen in liquid nitrogen immediately after collection and stored at –80°C until analysis. For the assay, samples were thawed on ice and microwaved for 8 s to halt enzyme activity.[4 5] cGMP concentrations were determined using a sensitive enzyme immunoassay kit (R&D Systems Europe, Abingdon, Oxon, UK) as described previously.[5] Protein was measured using Bradford reagent (Sigma-Aldrich, Poole, Dorset, UK) and results were expressed as saliva cGMP pmol (mg protein)$^{-1}$. Data were analysed using Friedman analysis of variance with Wilcoxon signed ranks post hoc testing as appropriate and Bonferroni correction for multiple comparisons as necessary.

There was no statistically significant variation in salivary cGMP either day-to-day or between time points in healthy volunteers. In patients, analysis of variance revealed a statistically significant change in cGMP (*P*=0.03) during anaesthesia and surgery with no change in salivary protein concentration. Post hoc analysis showed that cGMP increased significantly intraoperatively (*P*=0.023) and returned to preoperative levels following surgery (Fig. 1).

Comment

Our data show that concentrations of cGMP in saliva remain constant during normal activity and change during anaesthesia. Confounding variables were reduced to a minimum by choosing a group of patients who were essentially healthy, having minor obstetric surgery—thus all patients were female and of a very narrow age range. In addition, all the operations took place at a similar time of day, with the same anaesthetist, and the duration of the operation was similar (10–15 min). The anaesthetic regimen was standar-

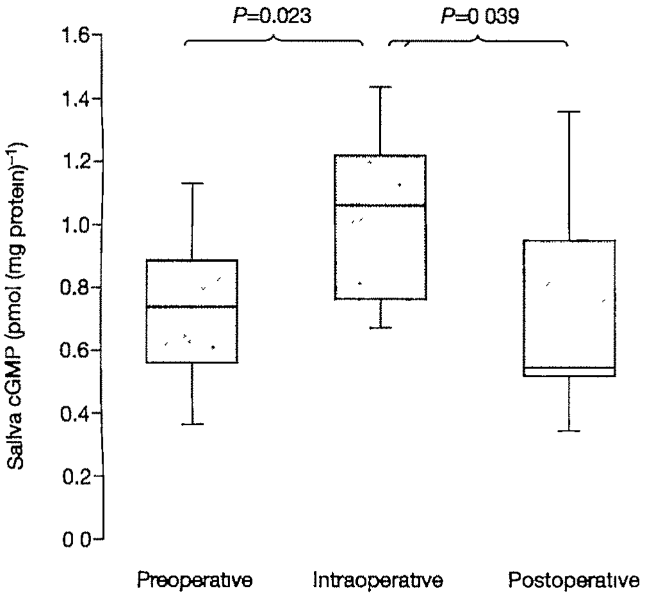


Fig 1 Changes in salivary cGMP in eight patients undergoing elective gynaecological surgery. Box and whisker plots show median, 25th and 75th percentile and range. *P* values refer to Wilcoxon signed ranks post hoc tests.

dized, with identical procedures for all patients, no premedication drugs and no opioid usage. Thus, changes in cGMP are more reliably related to anaesthesia and not other factors.

Studies in anaesthetized animals have shown decreases in cGMP within the central nervous system after halothane or isoflurane anaesthesia.[5] However, in the present study, salivary cGMP increased during anaesthesia compared with concentrations immediately pre-induction. This may be partially explained by nitric oxide synthase activity or haemoxygenase activity during anaesthesia. Both nitric oxide, produced by the action of nitric oxide synthase, and carbon monoxide, the product of haemoxygenase activity, are potent activators of soluble guanyl cyclase.[6]

The results of this study need to be extended to a larger study of various anaesthetic techniques to establish whether this is a common link for a mechanism of anaesthesia in humans. Also, the possible development of a 'real time' cGMP monitor is appealing and may allow an alternative technique for measuring depth of anaesthesia.

Acknowledgements

We acknowledge financial support from The Royal College of Anaesthetists, the Association of Anaesthetists of Great Britain and Ireland and the Chief Scientist Office in Scotland

References

1 Johns RA, Moscicki JC, DiFazio C. Nitric oxide synthase inhibitor dose-dependently and reversibly reduces the threshold for halothane anesthesia. *Anesthesiology* 1992; **77**: 779–84
2 Adachi T, Kurata J, Nakao S, *et al.* Nitric oxide synthase inhibitor does not reduce minimum alveolar concentration of halothane in rats. *Anesth Analg* 1994, **78**: 1154–7
3 Ichinose F, Huang PL, Zapol W. Effects of targeted neuronal nitric oxide synthase gene disruption and nitroG-arginine methylester on the threshold for isoflurane. *Anesthesiology* 1995; **83**: 101–8
4 Vulliemoz Y,Versoky M, Lapert M, Triner L. Effect of enflurane on cerebellar cGMP and and on motor activity in the mouse. *Br J Anaesth* 1983; **55**: 250–8
5 Galley HF, Le Cras AE, Logan SD, Webster NR. Differential nitric oxide synthase activity, co-factor availability and cGMP accumulation in the central nervous system during anaesthesia. *Br J Anaesth* 2001; **86**: 388–94
6 Morisaki H, Katayama T, Kotake Y, *et al.* Roles of carbon monoxide in leukocyte and platelet dynamics in rat mesenteric during sevoflurane anesthesia. *Anesthesiology* 2001; **95**: 192–9

British Journal of Anaesthesia 87 (5): 637–40 (2001)

Remifentanil or propofol for sedation during carotid endarterectomy under cervical plexus block

H. Krenn[1]*, E. Deusch[2], H. Jellinek[1], W. Oczenski[1] and R. D. Fitzgerald[1 3]

[1]Department of Anaesthesia and Intensive Care, City of Vienna Hospital Lainz, A-1130 Vienna, Austria.
[2]Department of Anaesthesiology and Intensive Care B, General Hospital, Vienna, Austria.
[3]Ludwig Boltzmann Institute for Economics of Medicine in Anaesthesia and Intensive Care, Vienna, Austria

**Corresponding author*

Background. During carotid endarterectomy under regional anaesthesia, patients often require medication to control haemodynamic instability and to provide sedation and analgesia.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Propofol and remifentanil are used for this purpose. However, the benefits, side-effects, and optimal dose of these drugs in such patients are unclear.

Methods. Sixty patients were included in a prospective, randomized, single blinded study. All patients received a deep cervical plexus block with 30 ml ropivacaine 0.75% and were randomized to receive either remifentanil 3 $\mu g\ kg^{-1}\ h^{-1}$ or propofol 1 mg $kg^{-1}\ h^{-1}$. The infusions were started after performing the regional block and were stopped at the end of surgery. Arterial pressure, ECG, ventilatory rate, and Pa_{CO_2} were measured continuously and recorded at predetermined times. Twenty-four hours after surgery, patient comfort, and satisfaction were also evaluated.

Results. In three patients, the infusion of remifentanil had to be stopped because of severe respiratory depression or bradycardia. No significant differences were found between the two groups in haemodynamic variables or sedative effects, but there was a significantly greater decrease in ventilatory frequency and increase in Pa_{CO_2} in the remifentanil group. The patient's subjective impressions and pain control were excellent in both groups.

Conclusion. As a result of the higher incidence of adverse respiratory effects with remifentanil and similar sedative effects, propofol is preferable for sedation during cervical plexus block in elderly patients with comorbid disease at the dosage used.

Br J Anaesth 2002; **89**: 637–40

Keywords: anaesthetic techniques, regional, cervical plexus; anaesthetics i.v., propofol; analgesics opioid, remifentanil; surgery, carotid endarterectomy; sedation

Accepted for publication: June 10, 2002

Propofol and remifentanil have been shown to be effective as adjuncts to regional anaesthesia in clinical trials.[1] However, no study has compared the effects of these drugs in patients with coexisting morbidity undergoing cervical plexus block.

We hypothesized that remifentanil 3 $\mu g\ kg^{-1}\ h^{-1}$ and propofol 1 mg $kg^{-1}\ h^{-1}$ would be equal in sedative, haemodynamic and respiratory effects, and improved patient acceptability of the technique. In a prospective, randomized, single blinded, and controlled study, we compared these drugs in patients undergoing carotid endarterectomy using deep cervical plexus block.

Methods and results

Following approval by the institutional ethics committee and having obtained written informed consent, 60 patients (ASA class III–IV) undergoing elective carotid endarterectomy were included in the study. Exclusion criteria were repeated operation, emergency surgery, or allergy to one of the drugs used. Using a computer-generated list (MS Excel 7.0), patients were randomized into two groups, to receive propofol or remifentanil.

Before the placement of the cervical plexus block, patients were monitored by five-lead electrocardiography, invasive arterial pressure, ventilatory frequency, and pulse oximetry. Deep cervical plexus block was performed using the single bolus-technique described by Winnie and colleagues[2] and a dose of 20 ml of ropivacaine 0.75%. Three millilitres of ropivacaine 0.75% were also injected below the inferior border of the mandible, and 7 ml were used to infiltrate the area of the skin incision. This was followed immediately by the start of an infusion of propofol 1 mg $kg^{-1}\ h^{-1}$ or remifentanil 3 $\mu g\ kg^{-1}\ h^{-1}$. Preoperatively, and at fixed points (P1=skin incision; P2=1 min after; P3=cross-clamp the carotid; P4=10 min later; P5=open the cross-clamp of the carotid; and P6=end of surgery), mean arterial pressure, heart rate, ventilatory frequency, Pa_{CO_2}, and sedative effect were noted. Only episodes of bradycardia not related to surgical stimulation were recorded. The effect of sedation was measured on a 5-point scale: (1) awake, (2) tired, (3) very tired, (4) asleep, but wakes up when called by name, or (5) only wakes up when the shoulder is shaken. At the end of surgery, the infusion was stopped and all patients were transferred to the post-anaesthesia care unit. On the first postoperative day, the patients' subjective impression of their pain control was recorded using a 10-point visual analogue scale (1=very good, 10=very bad).

Groups were compared using the Mann–Whitney *U* test. A *P* value of 0.05 was considered to be significant. Calculations were performed on a personal computer, using a standard software package (Winstat™ 3.0, Kalmia, US).

Sixty patients (median age 74 yr, range 54–83 yr) were investigated. In three patients in the remifentanil group, complications were encountered. In two cases, a bradycardia (heart rate between 30 and 35 beats min^{-1}) was

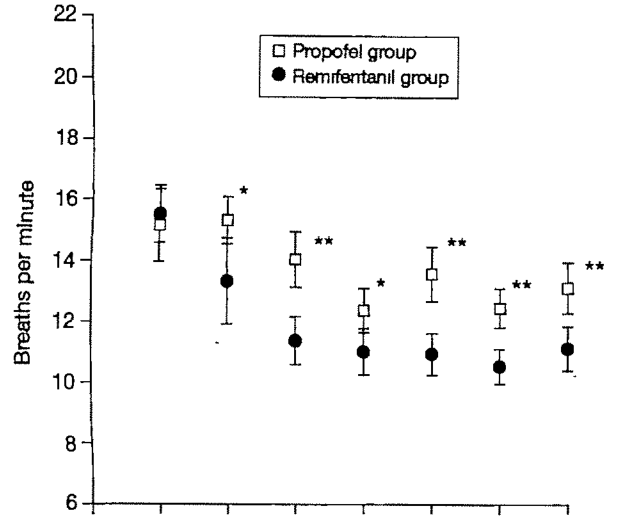


Fig 1 Respiration frequency preoperatively and at fixed points (P1=skin incision, P2=1 min after, P3=cross-clamping of the carotid; P4=10 min later; P5=end of cross-clamping of the carotid; P6=end of surgery) Data are shown as mean and range. *$P<0.05$, **$P<0.01$ between propofol group and remifentanil group at same time points.

detected a few minutes after starting the infusion. In one patient, sedation was excessive and respiratory depression (less than 6 bpm) occurred. The infusion of remifentanil was stopped in each instance and all patients recovered quickly, but were excluded from further evaluation.

After cross clamping of the carotid artery, one patient in the propofol group stopped breathing and lost consciousness. The patient's trachea was intubated and general anaesthesia was instituted. Postoperatively, a cerebrovascular accident was diagnosed and the patient was excluded from further evaluation. Four patients in the propofol group (13.8%) and three patients in the remifentanil group (11.1%) required additional local anaesthetic (lidocaine 0.5 %) around and within the carotid sheath.

Nitroglycerin 1–5 mg h^{-1} to treat hypertension was used in eight patients (26.6%) in the propofol group and seven patients (25.9%) in the remifentanil group. Nausea and vomiting occurred in five patients (16.7%) in the propofol group and seven patients (25.9%) in the remifentanil group. At no point were any differences found between groups in the mean arterial pressure, heart rate, or Sp_{O_2}. There was no difference in sedative effects between groups. Mean scores ranged between 1.67 and 1.97 in the remifentanil group and between 1.36 and 1.88 in the propofol group.

Mean (range) Pa_{CO_2} levels were almost the same preoperatively (remifentanil group 4.78 (4.27–5.35) kPa *vs* propofol group 4.85 (3.77–5.89) kPa). At points 1 and 2, Pa_{CO_2} increased significantly ($P<0.05$) in the remifentanil compared with the propofol group (5.5 (4.12–7.01) *vs* 4.92 (3.96–6.01) kPa and 5.67 (4.8–6.68) *vs* 5.18 (4.27–6.78) kPa). From point 3 to 6, this difference was even more pronounced ($P<0.01$) (P3: 5.66 (4.79–6.74) *vs* 5.19 (4.19–6.63) kPa; P4: 5.7 (4.8–6.7) *vs* 4.94 (4.03–6.7) kPa; P5: 5.66 (4.87–6.7) *vs* 5.03 (4.15–6.37) kPa; P6: 5.74 (4.53–6.76) *vs* 5.05 (4.11–6.12) kPa). Ventilatory frequency was found to be significantly different between the groups at every time point ($P<0.01$) (Fig. 1).

The patient's subjective impression of pain on a visual analogue scale was similar in both groups and showed good acceptance of the procedure (propofol group 1.67 (0.75); remifentanil group 1.77 (0.42)).

Comment

A large study, describing 1000 cervical plexus blocks for carotid endarterectomy, reported that 66% of patients required sedation during the operative period.[3] We compared two procedures, using dosages of propofol or remifentanil proven to be safe and effective in our institution, for sedation of patients with significant comorbidity. We found that both drugs supplied sufficient sedation, resulting in an excellent acceptance rate by the patients. However, adverse effects were higher in the remifentanil group.

The requirement for additional sedation during carotid endarterectomy results from: inability of the patient to move his head during surgery, causing pain in the cervical spine; or surgical manipulation in the area of the carotid sheath or under the mandible. Additionally, some patients are anxious. Such discomfort can result in adverse cardiovascular events, which are undesirable, as haemodynamic and respiratory instability are associated with a poor outcome after such surgery.[4]

Propofol is well established for sedation, as is remifentanil during regional anaesthesia.[1 5 6] However, there is no concordance about the optimal doses of these drugs in such circumstances and no data are available concerning patients of ASA class III–IV, the predominant group of patients undergoing this type of surgery. Lauwers and colleagues[1] used propofol 3 mg kg^{-1} h^{-1} or remifentanil 6 µg kg^{-1} h^{-1} for sedation during regional anaesthesia, and reported considerable side effects in both groups. Respiratory depression was reported to be more frequent in the remifentanil group. In another study, Lauwers and colleagues[6] compared three different doses of remifentanil (2.4 *vs* 4.2 *vs* 6 µg kg^{-1} h^{-1}) and found significant rates of respiratory depression, nausea, and sweating in all three groups. Using either propofol 4.5 mg kg^{-1} min^{-1} or remifentanil 6 µg kg^{-1} h^{-1}, Smith and colleagues[7] noted a greater degree of sedation in patients receiving propofol, whereas patients from the remifentanil group had more marked respiratory depression.

Mingus and colleagues[8] used higher doses of remifentanil 12 µg kg^{-1} h^{-1} and propofol 6 mg^{-1} kg h^{-1} in patients undergoing orthopaedic and urological surgery. These doses were increased by 50% when patients expressed discomfort, or decreased by 50% in the case of hypoventilation or haemodynamic instability. Remifentanil proved to be more effective than propofol in minimizing pain, but was associated with more respiratory depression and short-term nausea. In our study, 26% of patients in the remifentanil group suffered from nausea and vomiting compared with 17% in the propofol group.

The results reported by Mingus,[8] indicate that the remifentanil dose should be reduced to 6 μg kg^{-1} h^{-1} and to 3 μg kg^{-1} h^{-1} in elderly patients. However, our data suggest that in patients over 70 yr of age and classified as ASA III or IV, even a dose of 3 μg kg^{-1} h^{-1} can induce side effects. Thus, we believe that a further reduction in dosage is required. With a dose of propofol 1 mg kg^{-1} h^{-1}, we found stable haemodynamics, mild sedation, and no respiratory depression. Using the lowest remifentanil dose (3 μg kg^{-1} h^{-1}) recommended by Mingus and colleagues,[8] resulted in stable haemodynamics and mild sedation, but respiratory depression was significantly higher than in the propofol group.

We suggest that when using remifentanil for sedation in ASA III–IV patients undergoing carotid endarterectomy, the initial dose should be decreased to 1.5–2 μg kg^{-1} h^{-1} to minimize cardiovascular and respiratory complications in these elderly patients with significant comorbidity. A stepwise adaptation of the remifentanil dosage as proposed by Servin and colleagues[9] appears to be a promising alternative to a fixed dose regime. However, it remains to be determined whether a reduction in remifentanil dosage to avoid side effects leads to a loss of sedative and analgesic effects.

References

1 Lauwers MH, Vanlersberghe C, Camu F. Comparison of remifentanil and propofol infusion for sedation during regional anesthesia. *Reg Anesth Pain Med* 1998; **23**: 64–70

2 Winnie AP, Ramamurthy S, Durrani Z, Radonjic R. Interscalene cervical plexus block: a single-injection technic. *Anesth Analg* 1975; **54**: 370–5

3 Davies MJ, Silbert BS, Scott DA, Cook RJ, Mooney PH. Superficial and deep cervical plexus block for carotid artery surgery: a prospective study of 1000 blocks. *Reg Anesth* 1997; **22**: 442–6

4 Asiddao CB, Donegan JH, Whitesell RC, Kalbfleisch JH. Factors associated with perioperative complications during carotid endarterectomy. *Anesth Analg* 1982; **62**: 631–7

5 White PF, Negus JB. Sedative infusions during local and regional anesthesia: a comparison of midazolam and propofol. *J Clin Anesth* 1991; **3**: 32–9

6 Lauwers M, Camu F, Breivik H, *et al.* The safety and effectiveness of remifentanil as an adjunct sedative for regional anesthesia. *Anesth Analg* 1999; **88**: 124–40

7 Smith I, Avramov MN, White PF. A comparison of propofol and remifentanil during monitored anesthesia care. *J Clin Anesth* 1997; **9**: 148–54

8 Mingus ML, Monk TG, Gold MI, Jenkins W, Roland C. Remifentanil versus propofol as adjuncts to regional anesthesia in patients undergoing orthopedic or urogenital surgery. *J Clin Anesth* 1998; **10**: 46–53

9 Servin F, Desmonts JM, Watkins WD. Remifentanil as an analgesic adjunct in local/regional anesthesia and in monitored anesthesia care. *Anesth Analg* 1999; **89**: 28–32

British Journal of Anaesthesia **89** (**4**): 641–3 (2002)

BJA

CASE REPORTS

Spontaneous breathing combined with high frequency ventilation during bronchoscopic resection of a large tracheal tumour

M. Satoh*, **Y. Hirabayashi** and **N. Seo**

Department of Anaesthesiology, Jichi Medical School, Minamikawachi-machi, Tochigi, 329–0498, Japan

**Corresponding author*

A patient with learning difficulties had a large tracheal tumour at the carina that caused severe respiratory distress. I.v. anaesthesia with propofol, spontaneous breathing through a tracheal tube, and high frequency jet ventilation were successfully employed during bronchoscopic resection of the tumour.

Br J Anaesth 2002; **89**: 641–3

Keywords: airway, obstruction; anaesthetics i.v., propofol; complications, learning difficulties; complications, respiratory; intubation, tracheal; ventilation, high frequency jet

Accepted for publication: May 24, 2002

Primary tracheal tumours are uncommon.[1] The risk of respiratory distress is related to the size, location and shape of the tumour. Although resection of tracheal tumours in conscious patients using the fibreoptic bronchoscope is an effective and less invasive therapeutic option than thoracotomy, the associated management of the airway can prove difficult.

We describe a patient with learning difficulties who had severe airway obstruction secondary to a large tracheal tumour at the carina. In this case, spontaneous breathing during general anaesthetic, combined with high frequency jet ventilation (HFJV), was effective and facilitated the successful resection of the tumour through a tracheal tube.

Case report

A 28-yr-old man (weight, 83 kg; height, 178 cm) gave a 6-month history of a non-productive cough and wheezing. His medical history included learning difficulties secondary to neonatal hypoxic encephalopathy. His mental age was judged to be that of a 4-yr-old. As a result, he was unable to articulate his symptoms effectively and a physician initially treated him for an upper respiratory tract infection. He subsequently developed a sudden attack of severe respiratory distress early in the morning, and his family brought him to our hospital. A chest x-ray revealed a large tracheal tumour at the carina, which almost completely occluded the tracheal lumen. A thoracic CT scan demonstrated a 17.8 mm × 21.5 mm × 26.5 mm mass that was attached by a stalk to the anterior wall of the carina. Ninety-two per cent of the cross-sectional area of the trachea was obstructed by tumour (Fig. 1). The patient was kept in the left lateral decubitus position because his respiratory distress worsened in the right lateral decubitus and supine positions. Finger pulse oximetry (Sp_{O_2}) showed an oxygen saturation of 94–96% when he received oxygen 2 litres min^{-1} by face-mask. The patient refused arterial blood gas sampling. A decision was made to resect the tumour under general anaesthesia using the fibreoptic bronchoscope.

The patient was premedicated with famotidine 20 mg intravenously 30 min before induction of anaesthesia. On arrival in the operation room, his heart rate was 100 beats min^{-1}, arterial pressure was 145/75 mm Hg and Sp_{O_2} was 94%.

Prior to induction of anaesthesia, we prepared a jet ventilation catheter, and tracheostomy instruments in case of complications. The patient inhaled oxygen 100% for 10 min whilst in the left lateral decubitus position and was then turned to the supine position. Anaesthesia was induced with propofol 200 mg and manual ventilation via a facemask was started. Physical examination suggested a reduction in right chest wall movement at this time and the Sp_{O_2} fell from 100 to 95%. Succinylcholine 140 mg was administered to facilitate orotracheal intubation with a cuffed tube (internal diameter, 8.5 mm). The lungs were ventilated through the tracheal tube using a high frequency jet ventilator (driving pressure, 1.0 kgf cm^{-2}; I/E ratio, 0.33; rate, 60–120 min^{-1}; FI_{O_2}, 0.3–1.0). Bilateral chest wall movement was restored

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

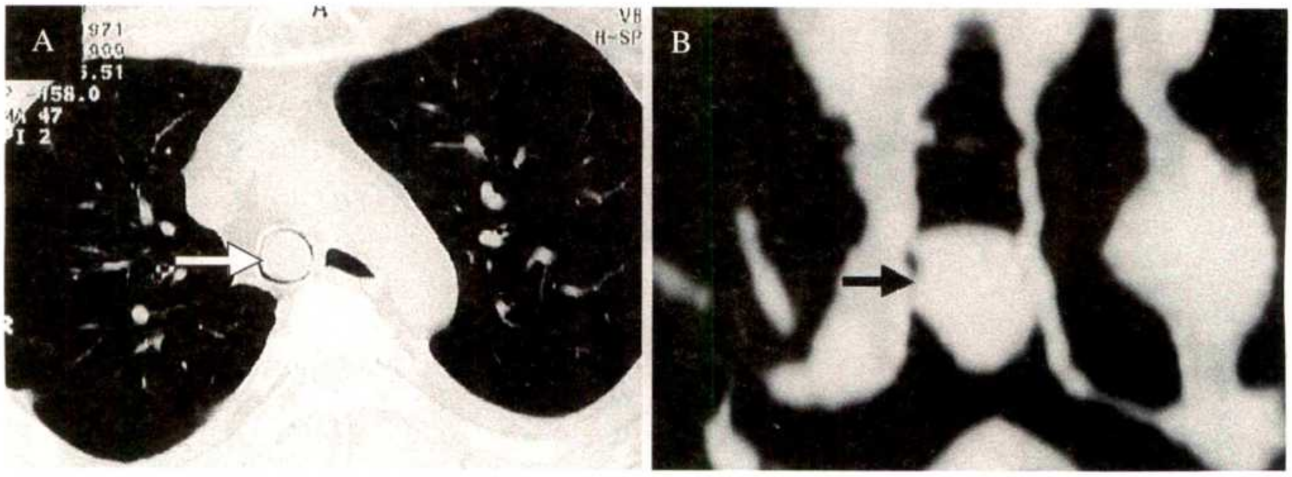


Fig 1 (A) Thoracic CT scans illustrating the presence of a tracheal tumour (white arrow); 92% of the tracheal cross sectional area was obstructed. The tumour stalk that attaches the lesion to the anterior wall of the carina is not evident in this image. The white arrow is on the right-hand side of the lung. (B) Reconstructed coronal image of thoracic CT scan demonstrating the tracheal tumour just above the carina (black arrow).

after spontaneous breathing had resumed. We decided to allow the patient to continue to breathe spontaneously. Anaesthesia was maintained with propofol 6 mg kg^{-1} h^{-1} and buprenorphine 0.2 mg intravenously.

Prior to the bronchoscopic procedure, the trachea was topically anaesthetized with lidocaine 2% (total dose, 400 mg) via the tracheal tube. The operation was performed with a fibreoptic bronchoscope (external diameter, 6 mm) via the tracheal tube. HFJV was then performed through a 10-Fr suction catheter, which was passed through the same tracheal tube for 2 cm into the left main bronchus. Whenever the Sp_{O_2} fell below 95%, the bronchoscopic procedure was temporarily halted and ventilation was gently assisted. This occurred three times during HFJV. As the Sp_{O_2} also fell if the driving pressure was reduced, we set the driving pressure at 1.0 kgf cm^{-2}. As a result, the Sp_{O_2} did not then fall below 93% at any stage. Arterial blood pressure remained at 100–120/45–60 mm Hg whilst the heart rate was between 80 and 100 beats min^{-1}. There were no ECG changes throughout the procedure. Arterial blood gas analysis revealed a Pa_{O_2} of 10.8 kPa, a Pa_{CO_2} of 7.8 kPa and a pH of 7.31 when the Sp_{O_2} fell to its lowest value of 93% during the operation.

The stalk of the tumour was cauterized. The surgeons then removed the tumour, together with the tracheal tube, using a basket catheter because the tumour was too large to pass through the tracheal tube. Following successful removal of the tumour and the tracheal tube, the patient developed laryngospasm. Vecuronium bromide 10 mg and hydrocortisone sodium succinate 500 mg were administered intravenously and another tracheal tube (internal diameter, 7.5 mm) was inserted. The surgeons confirmed complete resection of the tumour by fibreoptic bronchoscopy. Chest wall movement was symmetrical soon after the operation had been completed and the lungs were artificially ventilated for a further 30 min. The second tracheal tube was removed following administration of neostigmine 2.5 mg and atropine 1.0 mg to antagonize any residual neuromuscular block. The operation lasted 70 min. The total durations of anaesthesia and HFJV were 150 min and 53 min, respectively. The patient developed no further airway problems following the surgery.

Discussion

The first challenge of this clinical case was the method to be used to control the airway. Adults usually undergo fibreoptic examination whilst awake since this is safer than being under general anaesthetic. However, in children or individuals with significant learning difficulties, this approach is problematic. Because of the patient's limited intellectual capacity, we judged that it would prove impossible to use a fibreoptic technique for the surgery whilst he was awake. In addition, the surgeons informed the anaesthetists that several patient positions, including prone, lateral, semierect and supine positions, would be required during bronchoscopic resection of the tumour. We therefore decided to use general anaesthesia and a tracheal tube rather than a laryngeal mask airway for this patient. In view of the proposed surgical procedure, we used the largest tracheal tube available. Using a tracheal tube does carry a risk of massive bleeding from the tracheal tumour in such cases. However, in this patient, the CT scan demonstrated that the tumour was located at the carina and that there was sufficient distance between the vocal cords and the tumour to allow safe insertion of a tracheal tube.

The second challenge of the case related to the method of ventilation used during the bronchoscopic procedure. Spontaneous breathing has frequently been recommended during anaesthesia in such circumstances, to avoid airway obstruction resulting from muscle paralysis or positive pressure ventilation.[2] In our patient, we noted that movement of the right chest wall worsened during positive pressure ventilation on induction of anaesthesia. It was thought that right main bronchus obstruction had been induced by the artificial ventilation, resulting in dynamic hyperinflation. We therefore allowed spontaneous breathing during surgery and applied HFJV in order to assist ventilation effectively.[2] The disadvantages of this technique can include ineffective ventilation and a potential hindrance to surgery. Bronchoscopy indicated that the spherical tumour almost completely blocked the right main bronchus and so the HFJV catheter was passed about 2 cm into the left main bronchus. In this way, we were able to prevent hyperinflation of the right lung and allow optimal access to the surgical field.

The other method of managing hypoxaemia during one-lung ventilation is continuous positive airway pressure (CPAP). However, it has been reported that CPAP does not generate sufficient alveolar oxygen tension in the non-ventilated lung to prevent hypoxaemia in patients with bronchial obstruction.[3] Studies by Slinger and colleagues[4 5] reported that the side of the ventilated lung was an important factor in this respect; the efficiency of oxygenation and of gas exchange was better when the right lung rather than the left lung was ventilated during one-lung ventilation. Although in this case only the left lung was ventilated, we were able to use HFJV with a 10-Fr suction catheter and a $F\text{I}_{O_2}$ of only 0.3 during the procedure. The effects of HFJV on oxygenation and gas exchange were not determined since neither the flux nor the pressure were measured. However, we considered that HFJV supported breathing effectively and did not hinder spontaneous breathing in this case.

Helium–oxygen mixtures are commercially available and may be useful in the emergency department to treat patients with airway obstruction.[6 7] Breathing a mixture of helium and oxygen leads to a reduction in the resistance to flow within the airways, and consequently results in a decrease in the work involved in breathing. Whether awake or asleep, our patient showed a deterioration in his condition when his position was changed. Although helium would have been potentially useful, it is not available for such treatment in Japan. It might have been an excellent method of allowing spontaneous breathing in combination with HFJV.

The third aspect of this case for consideration was the anaesthetic agents used. Anaesthetic induction with inhalational agents is usually regarded as the technique of choice in view of its safety.[2] Nevertheless, adverse events have been reported with this technique.[8] Using the i.v. anaesthetic agent, propofol, we were able to maintain the depth of anaesthesia more readily than with inhaled anaesthetic agents. It has been reported that the respiratory depressant effects of propofol 6 mg kg^{-1} h^{-1} are clinically acceptable and we selected an i.v. anaesthetic technique for these reasons.[9]

We applied topical anaesthetic to the trachea and bronchus in order to prevent adverse reflexes during the fibreoptic bronchoscopy. The surgeons removed the tumour with the tracheal tube, contrary to our expectations. Unfortunately, the larynx had been insufficiently anaesthetized to prevent laryngospasm after extubation.

In summary, this case report describes the anaesthetic management of a patient with learning difficulties who successfully underwent bronchoscopic resection of a large tracheal tumour. During the procedure, i.v. anaesthesia with propofol and spontaneous breathing, combined with HFJV, allowed effective management of the airway.

References

1 Gelder CM, Hetzel MR. Primary tracheal tumours: a national survey. *Thorax* 1993; **48**: 688–92

2 Narang S, Harte BH, Body SC. Anesthesia for patients with a mediastinal mass. *Anesthesiol Clin North Am* 2001; **19**: 559–79

3 Slinger P, Scott WA. Arterial oxygenation during one-lung ventilation. A comparison of enflurane and isoflurane. *Anesthesiology* 1995; **82**: 940–6

4 Slinger P, Suissa S, Adam J, Triolet W. Predicting arterial oxygenation during one-lung ventilation with continuous positive airway pressure to the nonventilated lung. *J Cardiothorac Anesth* 1990; **4**: 436–40

5 Slinger P, Suissa S, Triolet W. Predicting arterial oxygenation during one-lung anaesthesia. *Can J Anaesth* 1992; **39**: 1030–5

6 McGee DL, Wald DA, Hinchliffe S. Helium–oxygen therapy in the emergency department. *J Emerg Med* 1997; **15**: 291–6

7 Chevrolet JC. Helium oxygen mixtures in the intensive care unit. *Crit Care* 2001; **5**: 179–81

8 Ferrari LR, Bedford RF. General anesthesia prior to treatment of anterior mediastinal masses in pediatric cancer patients. *Anesthesiology* 1990; **72**: 991–5

9 Goodman NW, Black AM, Carter JA. Some ventilatory effects of propofol as sole anaesthetic agent. *Br J Anaesth* 1987; **59**: 1497–503

British Journal of Anaesthesia **89** (**4**): 644–7 (2002)

Postoperative use of a cough-assist device in avoiding prolonged intubation

W. A. Marchant and R. Fox*

The Royal National Orthopaedic Hospital Trust, Brockley Hill, Stanmore, Middlesex HA7 4LP, UK
**Corresponding author*

Postoperative management following major surgery in patients with neuromuscular disorders associated with scoliosis is frequently complicated by sputum retention and ventilatory failure. This report demonstrates the successful perioperative management of an 11-yr-old boy with type II spinal muscular atrophy undergoing a single-stage posterior spinal fusion procedure. Use of an MI-E device was able to successfully treat sputum retention and avoid a tracheostomy.

Br J Anaesth 2002; **89**: 644–7

Keywords: airway, reflexes; complications, muscular atrophy; complications, respiratory; cough; infections, pulmonary; lung, mucus; scoliosis; ventilation, postoperative

Accepted for publication: May 31, 2002

Patients with neuromuscular disorders associated with scoliosis often present when restrictive respiratory failure is developing. Postoperative management following major surgery is frequently complicated by sputum retention and ventilatory failure, which may lead to prolonged intensive care episodes, tracheostomy formation with attendant complications, and death.

Ventilatory failure can now be easily managed with the use of non-invasive ventilation. This case report shows that the treatment of postoperative sputum retention, and avoidance of tracheostomy, can also be aided by using mechanical insufflation-exsufflation.

Case report

An 11-yr-old boy with type II spinal muscular atrophy (SMA) presented for assessment before corrective spinal scoliosis surgery. He had been wheelchair-bound since infancy because of his disease. He required help with feeding and personal hygiene, which was made more complicated by his obesity (BMI 34.7). His last chest infection requiring hospital admission was at the age of 7 yr, for which he did not require mechanical ventilation. Subsequent chest infections were managed at home, and the year preceding surgery he had been relatively free of them.

His cough reflex was intact but very poor. Parental reports stated that coughing episodes often interrupted his sleep, sometimes requiring assisted coughing by his mother to aid clearance of secretions. He snored at night but did not suffer from early morning headaches, daytime somnolence, or apnoeas. His school progress was considered normal.

On clinical examination, he weighed 76 kg. Cardiovascular and respiratory examinations were unremarkable. A transthoracic echocardiogram was normal. His forced expiratory volume in 1 s (FEV_1) was 0.92 litres, and forced vital capacity (FVC) was 0.97 litres (35% predicted). He had a short neck and poor mouth opening. Radiographic examination revealed a thoracic scoliosis with a Cobb angle of 101°.

A sleep study performed using transcutaneous carbon dioxide and oxygen electrodes combined with pulse oximetry, showed a baseline partial pressure of oxygen of 68 torr (9.0 kPa), intermittently dipping to 38 torr (5.0 kPa), and a baseline partial pressure of carbon dioxide of 49 torr (6.5 kPa), intermittently rising to 68 torr (9.0 kPa). On the basis of this study he was sent for a respiratory opinion, from where he was established on nocturnal non-invasive ventilation. Five months later, he represented for posterior fusion and instrumentation surgery for his scoliosis. This was to aid in his posture maintenance whilst sitting in his wheelchair, and for pain control. Repeat lung function tests at this time, showed a minimal improvement with an FEV_1 of 1.18 litres, and an FVC of 1.26 litres. It was decided not to repeat the sleep study as the patient was now established on nocturnal non-invasive ventilation, and it was felt that no useful information would be gained.

A gaseous induction was performed using sevoflurane, as venous access was predicted to be difficult. Vecuronium was given to aid tracheal intubation. He was a grade III Cormack and Lehane direct laryngoscopy view. A laryngeal mask airway was inserted and his trachea was subsequently intubated through it using a fibreoptic laryngoscope. Anaesthesia was maintained using oxygen, nitrous oxide,

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

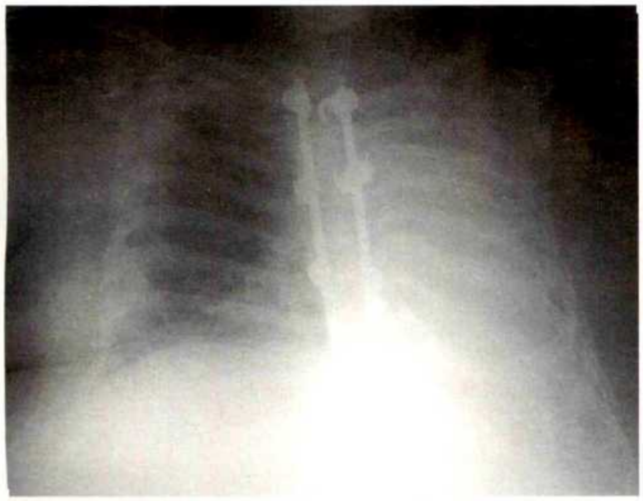


Fig 1 Chest radiograph showing a small right-sided pleural effusion and whiteout on the left side.

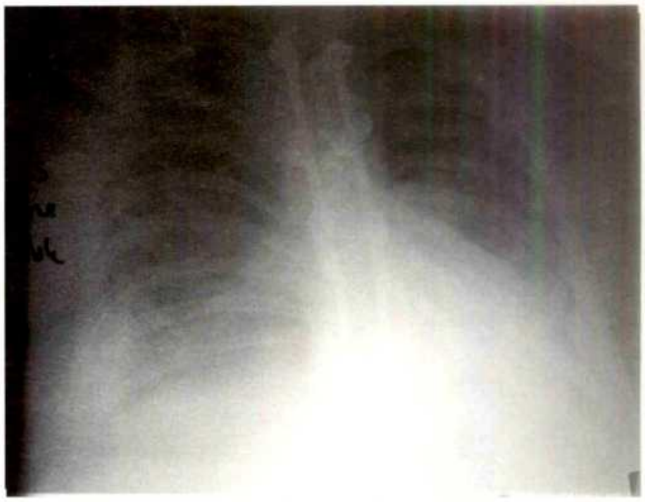


Fig 2 Chest radiograph taken 36 h after initiation of cough-assist device.

and isoflurane. Intermittent positive pressure ventilation was used throughout the procedure. His spinal column was fused from the fourth thoracic vertebra down to the sacrum. Estimated blood loss was 3 litres. The operating surgeon sited an epidural between the seventh and eighth thoracic vertebrae before wound closure.

After surgery, the patient was electively ventilated on the intensive care unit for 24 h so that the neuromuscular blocking agent could wear off, haemostasis could be ensured, and good analgesia via the epidural achieved. A continuous infusion of 0.125% bupivacaine was run through the epidural catheter at a rate of 4 ml h^{-1}. Regular acetaminophen suppositories were also used for analgesia. The tracheal tube was removed and the patient was placed immediately on to his own non-invasive ventilator (Nippy). His ventilatory frequency was 18 bpm with adequate chest expansion and arterial oxygen saturations of 98% on 35% oxygen.

The following day, his arterial partial pressure of oxygen was 86 torr (11.4 kPa) on 35% oxygen, and he had moderate amounts of loose secretions on his chest. He remained on non-invasive ventilation, with his pain well controlled. His cough remained very poor and he required manual assistance with coughing, although sputum clearance was inadequate. He had clinical and radiological evidence of left lower lobe collapse and consolidation. The epidural infusion was discontinued on the third postoperative day and regular acetaminophen continued.

During the following 3 days his chest continued to deteriorate. He desaturated intermittently and became very dependent on his non-invasive ventilator, desaturating down to 82% when removing the mask to eat. By this time, his secretions had become very thick. He was being treated with saline nebulizers, antibiotics (cefuroxime), and intensive physiotherapy. The patient remained free from pain.

The following day, his chest radiograph (Fig. 1) showed a small right-sided pleural effusion and almost whiteout on the left side. Clinically, he remained on a non-invasive ventilator maintaining saturations greater than 95% on about 40% oxygen. At this stage he was to undergo an elective tracheostomy the next day. The cough-assist device was then tried. The patient tolerated it very well and it was able to assist him bringing thick secretions into his mouth from his chest.

As he was now able to clear secretions from his chest, the tracheostomy was delayed. The cough-assist device was used every 4 h and his condition continued to improve, as did the appearance of his chest radiograph (Fig. 2). Six days after first using the cough-assist machine, he progressed from requiring continuous non-invasive ventilation, to only needing nocturnal respiratory support, as in the preoperative phase. Three days later, he was able to return to the ward (17 days after surgery) and was discharged home well, 27 days later.

Discussion

SMA type II is an inherited disorder affecting the peripheral motor neurones without upper motor neurone involvement. The disease tends to be hereditary, usually autosomal recessive. Children with SMA type II usually survive into adolescence or even early adulthood. Patients with severe neuromuscular disorders, such as SMA and Duchenne muscular dystrophy, present for surgical repair of scoliosis for a variety of reasons. Often the patient is unable to maintain a sitting position in their wheelchair, and the surgery is performed with the aim of improving the child's posture, general management, and discomfort. This patient population also may suffer with pain, often alleviated by surgical correction of their scoliosis. Poor respiratory function secondary to respiratory muscle weakness, a hallmark of these children, is not reversible by correcting the scoliosis but aids in slowing its progress. These children are therefore at a high risk of developing postoperative respiratory problems. The inability to effectively expectorate airway secretions is the main cause of respiratory failure and death for these patients.[1]

Nasal intermittent positive pressure ventilation (NIPPV) can be life-saving in patients with established ventilatory failure.[2] It has been shown that in hypercapnic patients with Duchenne muscular dystrophy, NIPPV is likely to increase survival in some patients by 5 yr or more.[3] In neuromuscular disease, hypoventilation first occurs during sleep as a result of a reduction in intercostal and accessory muscle tone, and a decrease in ventilatory drive which is most prominent during rapid eye movement (REM) sleep. This then progresses to daytime ventilatory failure and ultimately, cor pulmonale. Our patient had evidence of nocturnal hypoventilation on his sleep study, although he denied any symptoms of sleep apnoea on direct questioning. It was for this reason that he was referred for a respiratory opinion, and established on nocturnal NIPPV. Having had a 5-month period of nocturnal ventilation, his parents said that he now slept better, and was brighter in the mornings.

Adequate expiratory muscle function is critical for clearing airway secretions and bronchial mucous plugs. During periods of respiratory tract infection (RTI) or profuse airway secretion, peak cough expiratory flows (PCEFs) must be adequate to prevent mucous plugging and pulmonary complications. The vital capacity (VC), FVC, and PCEF are decreased during RTIs because of fatigue, respiratory musculature weakening, and mucous plugging.[4] During a normal adult cough, just over 2 litres of air is expelled at flows of up to 20 litre s^{-1}.[5] High thoraco-abdominal pressures are needed to generate effective cough flows on glottic opening, and the effectiveness of mucus clearance is largely dependent on the magnitude of the PCEF.[6] Both inspiratory and expiratory muscle weakness can cause cough flows to decrease. This can be further decreased by bulbar problems with incomplete or weak glottic closure. Cough flows less than 2.7 litre s^{-1} have been found to be ineffective in clearing secretions.[7]

Postural drainage and chest percussion are used routinely to mobilize airway secretions, although they are not always possible to use and are effort-intensive. They were used in the case of our patient but were not effective, because of his size, in aiding mucus clearance. Using deep lung insufflations, the maximum inspiratory capacity in patients with neuromuscular disease can be achieved. The insufflations may be delivered via a mouthpiece or nasal interface from a ventilator or manual resuscitator. The increase to maximum inspiratory capacity leads to a significant increase in the assisted PCEF.[7] There are many techniques of manually assisted coughing. For patients with less than 1.5 litre of VC (as in the case of our patient) efficacy is enhanced by preceding an assisted exsufflation with a deep insufflation. Manually assisted coughing requires a cooperative patient, good coordination between the patient and caregiver, and adequate physical effort by the caregiver. When inadequate, the most effective alternative for generating optimal PCEF and clearing deep airway secretions is the use of mechanical insufflation-exsufflation (MI-E).[8]

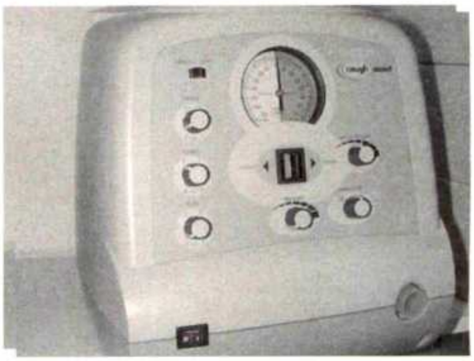


Fig 3 Emerson CoughAssist™ Mechanical In-Exsufflator.

As early as 1953, portable devices for delivering MI-E directly to the airway via a mouthpiece, mask, or tracheal tube were being manufactured.[9] The efficacy of MI-E was demonstrated both clinically and on animal models in the expulsion of bronchoscopically inserted foreign bodies.[10] The volume of air and PCEF exsufflated during MI-E are comparable with those expulsed during normal adult coughing. In one study of 46 neuromuscular ventilator users, PCEFs of more than 7.5 litre s^{-1} were obtained using MI-E, as compared with 4.3 litre s^{-1} using a maximum inspiratory capacity manoeuvre followed by manual assistance with abdominal compression.[11] Early work has shown that in addition to the clearing of pulmonary infiltrates and atelectasis, MI-E can increase FVC by up to 55% in patients with paralytic restrictive pulmonary conditions.[12] The use of MI-E through a tracheostomy tube has been demonstrated to be effective in reversing acute atelectasis associated with airway secretions, although PCEF were shown to be greater when MI-E was applied via a mask. A recent study has confirmed the value of MI-E in decreasing hospitalization rates for respiratory complications of neuromuscular disease.[13]

The MI-E that we used is the Emerson CoughAssist™ Mechanical In-Exsufflator (J.H. Emerson Co., Cambridge, MA, USA) (Fig. 3). It has both a manual and an automatic mode, such that cycling from insufflation to exsufflation may be manually controlled or automatic. One treatment consists of about five cycles followed by a period of normal breathing or ventilator use for about 30 s to avoid hyperventilation. Each cycle comprises insufflation, then exsufflation, followed by a pause, at which the machine returns to atmospheric pressure. The pressures are generated by a two-stage centrifugal blower.[14] The positive and negative pressures may be set for insufflation and exsufflation, up to a maximum of 60 cm H_2O. Each insufflation and exsufflation is usually 2–3 s.

Use of the MI-E has been found to be safe. One study found no adverse effects encountered in more than 2000 courses of MI-E, the majority of which were in patients with intrinsic lung disease.[12] Transient appearance of blood-streaked sputum, probably originating from the bronchial wall sites of detachment of mucous plugs, may occur. Animal studies have revealed no evidence of parenchymal damage, haemorrhage, alveolar tears, or emphysematous blebs in the lungs of animals treated with MI-E.[10] Borborygmus and abdominal distension are infrequent and eliminated by decreasing insufflation pressures, and aspiration of gastric contents has not been reported.

In summary, this case report demonstrates the successful perioperative management of a child with SMA undergoing a single-stage posterior spinal fusion procedure. Use of an MI-E device was able to successfully treat sputum retention and avoid a tracheostomy.

References

1 Bach JR, Rajaraman R, Ballanger F, *et al.* Neuromuscular ventilatory insufficiency: the effect of home mechanical ventilator use vs. oxygen therapy on pneumonia and hospitalization rates. *Am J Phys Med Rehabil* 1998; **77**: 8–19

2 Vianello A, Bevilacqua M, Salvador V, Cardaioli C, Vincenti E. Long-term nasal intermittent positive pressure ventilation in advanced Duchenne's muscular dystrophy. *Chest* 1994; **105**: 445–8

3 Simonds AK, Muntoni F, Heather S, Fielding S. Impact of nasal ventilation on survival in hypercapnic Duchenne muscular dystrophy. *Thorax* 1998; **53**: 949–52

4 Mier-Jedrzejowicz A, Brophy C, Green M. Respiratory muscle weakness during upper respiratory tract infections. *Am Rev Respir Dis* 1998; **138**: 5–7

5 Leith DE. Cough. In: Brain JD, Proctor D, Reid L, eds. *Lung Biology in Health and Disease: Respiratory Defence Mechanisms, Part 2*. New York, NY: Marcel Dekker, 1977; 545–92

6 King M, Brock G, Lundell C. Clearance of mucus by simulated cough. *J Appl Physiol* 1985; **58**: 1776–85

7 Kang S-W, Bach JR. Maximum insufflation capacity. *Chest* 2000; **118**: 61–5

8 Bach JR. Update and perspective on non-invasive respiratory muscle aids. Part 2: the expiratory aids. *Chest* 1994; **105**: 1538–44

9 Segal MS, Salomon A, Herschfus JA. Alternating positive-negative pressures in mechanical respiration (the cycling valve device employing air pressures). *Dis Chest* 1954; **25**: 640–8

10 Bickerman HA. Exsufflation with negative pressure: elimination of radiopaque material and foreign bodies from bronchi of anesthetized dogs. *Arch Intern Med* 1954; **93**: 698–704

11 Bach JR. Mechanical insufflation-exsufflation. Comparison of peak expiratory flows with manually assisted and unassisted coughing techniques. *Chest* 1993; **104**: 1553–62

12 Barach AL, Beck GJ. Exsufflation with negative pressure: physiologic and clinical studies in poliomyelitis, bronchial asthma, pulmonary emphysema and brochiectasis. *Arch Intern Med* 1954; **93**: 825–41

13 Tzeng AC, Bach JR. Prevention of pulmonary morbidity for patients with neuromuscular disease. *Chest* 2000; **118**: 1390–6

14 Emerson. CoughAssist™ User's Guide. J.H. Emerson Co., Cambridge, MA, USA

British Journal of Anaesthesia **89** (**4**): 647–50 (2002)

Bilateral pleural effusions: unexpected complication after left internal jugular venous catheterization for total parenteral nutrition

H. G. W. Paw

Intensive Care Unit, York District Hospital, Wigginton Road, York YO31 8HE, UK

Bilateral pleural effusions occurred after total parenteral nutrition was administered via a left internal jugular venous line. The most likely explanation for the fluid passage into both pleural cavities was migration of the tip of the catheter from within the vein into the mediastinum. Fluid can pass into both pleural cavities via anatomical communications, yet to be described, which exist between the two pleural cavities.

Br J Anaesth 2002; **89**: 647–50

Keywords: complications, respiratory; equipment, catheters central venous; fluids, i.v.; lung, damage; lung, interpleural space; surgery, laparotomy

Accepted for publication: May 8, 2002

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

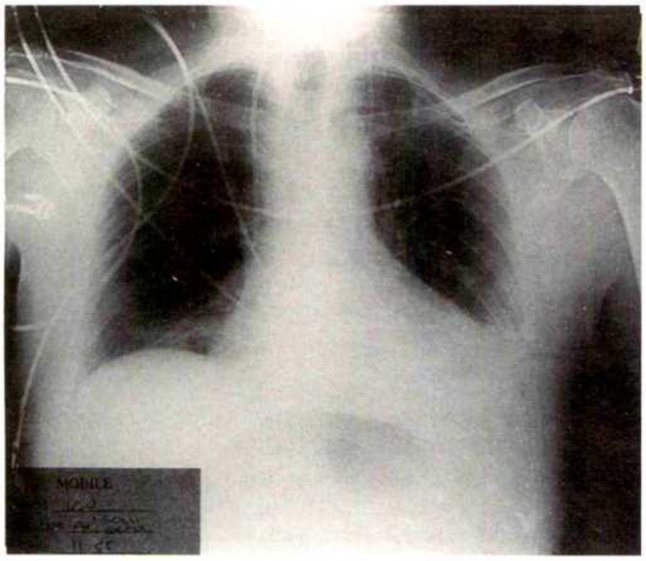


Fig 1 Chest x-ray showing the tip of the right internal jugular line in a position consistent with placement within the superior vena cava, and the tip of the left internal jugular line in a position consistent with placement within the left bronchiocephalic vein.

Central venous catheterization can cause various complications, which are on the whole simple to explain with our current knowledge of anatomy. This case report, however, describes a complication occurring after internal jugular venous catheterization, which is difficult to explain with our current knowledge of anatomy. Reports of ipsilateral pleural effusion following misplacement of a central venous catheter are not unusual. However, communications between the two pleural cavities are not known. A similar case of bilateral pleural effusions following a left internal jugular venous cannulation has been reported.[1] A second case of bilateral pleural effusions following an attempted right subclavian venous cannulation has also been reported.[2] No explanation was provided for the complication in either paper.

Case report

A 62-yr-old man with a 2-day history of severe abdominal pain associated with vomiting was admitted to hospital as an emergency. He underwent an uneventful laparotomy on the same day. The operative findings were a 50-cm section of infarcted terminal ileum and 10 cm of ischaemic terminal ileum in continuity with the caecum. A small bowel resection and a limited right hemicolectomy were done. A thoracic epidural was placed for postoperative pain relief. A four-lumen catheter was inserted uneventfully into the right internal jugular vein. A portable anteroposterior chest x-ray confirmed the position of the line to be satisfactory and a good central venous pressure (CVP) trace was measured with a transducer. Because this patient had a complex medical history (multiple previous myocardial infarctions and a pulmonary embolus after an inguinal hernia repair), he was admitted to intensive care after surgery. The tracheal tube was removed the next morning and transferred to the high dependency unit (HDU).

On the third day of his hospital admission, a decision was made to start parenteral feeding as he was not expected to absorb enteral feed. An experienced senior house officer in anaesthesia placed an 18-gauge single lumen 15 cm catheter LeaderCath (Vygon UK Ltd., Gloucestershire, UK) into the left internal jugular vein. The entry point was midway from a line drawn between the suprasternal notch and the mastoid process. Initial cannulation of the vein was not easy, but blood was eventually aspirated via the needle. The guidewire threaded easily and blood could be aspirated through the catheter. At this point the patient complained of feeling a lump in his throat. The anteroposterior chest x-ray showed the tip of the catheter in a position consistent with placement within the left brachiocephalic vein (Fig. 1) and total parenteral nutrition (TPN) was started. There was no reason to doubt the position of the catheter in the vein and the pressure in the cannula was not measured to ensure that a CVP trace was present. The patient made a good recovery from his operation, and on the 4th day he was discharged from HDU to the ward.

Two days after the commencement of TPN, the patient was noted to be more breathless. High flow oxygen via a face mask was needed to keep his arterial oxygen saturation above 90%. Arterial blood gas analysis showed a pH of 7.33, a carbon dioxide tension ($Pa_{\mathrm{CO_2}}$) of 7.6 kPa, and an oxygen tension ($Pa_{\mathrm{O_2}}$) of 7.1 kPa while breathing 60% oxygen. A chest x-ray showed bilateral pleural effusions (Fig. 2). Ultrasonography of the thorax confirmed large bilateral pleural effusions. A 20-F chest drain was placed into each side of the chest. Over 2 litres of white, milky fluid was drained from the right-hand side and another 2 litres of a similar milky coloured fluid was drained from the left-hand side. As the fluid was suspected to contain TPN, the infusion was immediately stopped. It was not possible to aspirate blood, air or fluid from the venous cannula. Biochemical analysis of the drained fluid from both sides suggested that it was TPN. The two samples of drained fluid had glucose concentrations of 20.0 mmol litre^{-1} and 22.0 mmol litre^{-1}. The patient's blood glucose was 4.9 mmol litre^{-1} at the time. The glucose concentration of the TPN was 397 mmol litre^{-1}. The drained fluid was presumably a mixture of TPN and pleural fluid. Before the removal of the catheter, 60 ml of radiographic contrast was injected. An immediate chest x-ray showed contrast in the upper mediastinum (Fig. 3). However, a repeat chest x-ray 45 min later showed no contrast in the chest. It was assumed to have drained from the chest drains.

After placing the chest drains, arterial blood gas analysis showed a pH of 7.38, $Pa_{\mathrm{CO_2}}$ of 6.2 kPa and $Pa_{\mathrm{O_2}}$ of 14.0 kPa on 60% oxygen via a facemask. The chest radiograph showed resolution of both pleural effusions and re-expansion of both lungs. Antibiotic treatment with cefotaxime and

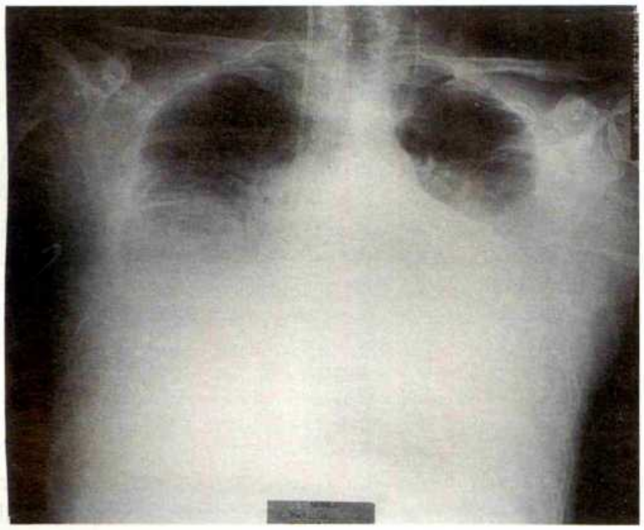


Fig 2 Chest x-ray showing bilateral pleural effusions.

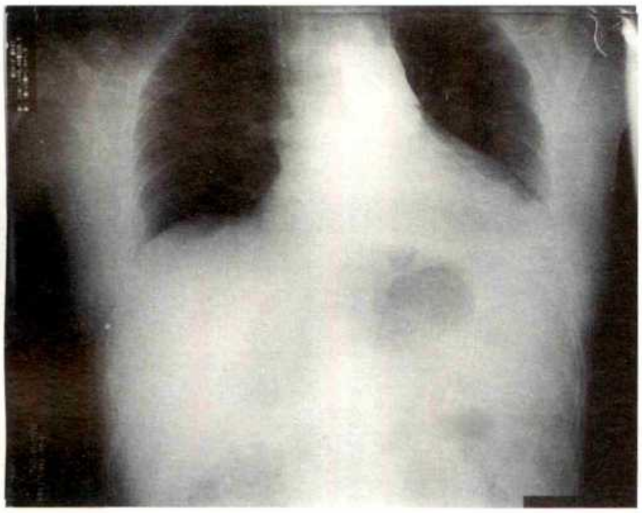


Fig 3 Chest x-ray showing the spill of contrast into the upper mediastinum immediately following its injection into the left catheter.

metronidazole was continued, which had been started empirically after surgery. Over the next 3 days, further drainage from both chest drains was minimal and the patient remained apyrexial and well. The chest drains were removed after 3 days and the patient was finally discharged from hospital 12 days after the laparotomy.

Discussion

This is a case of bilateral pleural effusions after attempted left internal jugular venous cannulation. The most likely explanation of the bilateral effusions is the passage of TPN from the displaced catheter into the mediastinum and then into both pleural cavities via anatomical communications between them. Fortunately, the patient recovered uneventfully.

Reports of ipsilateral pleural effusion following misplaced central venous catheters are not unusual.[3 4] Possible channels communicating between the peritoneal cavity and the pleural cavity have also been reported.[5] However, no communications are known between the two pleural cavities. Hence, this case is unusual. Two similar cases of bilateral pleural effusions following attempted central venous catheter placement have been reported,[1 2] although no explanations were suggested for the complication.

I.v. nutrition in patients who are unable to start enteral nutrition is a well-established clinical technique. Because of their hypertonicity, these solutions must be given into a vessel with rapid blood flow and adequate mixing. This usually involves using a central venous catheter. Complications of central venous catheter placement include pneumothorax, pleural effusion, thrombophlebitis, brachial plexus injury, mediastinal haematoma and arterial cannulation.[6]

Percutaneous insertion of central venous catheters are usually done by using surface anatomical landmarks (palpable or visible structures) with known relationships to the desired vein. The infraclavicular approach to the subclavian vein requires finding the correct location of the clavicle, suprasternal notch and sternocleidomastoid–clavicular triangle landmarks, proper positioning of the patient and operator and correct venepuncture point depth, direction and insertion angle. Similarly, the various approaches to the internal jugular vein require thorough knowledge of this vein's course in relation to the sternocleidomastoid muscle and carotid artery.

Newer techniques, such as portable ultrasound devices, provide bedside imaging of the central veins during catheter placement.[7 8] The advantages of ultrasound-guided central venous catheter placement include detection of anatomical variations, exact vessel location, avoidance of central veins with pre-existing thrombosis that may prevent successful catheter placement and guidance of both guidewire and catheter placement after initial needle insertion. Although there is no doubt that these devices improve the safety of central venous catheter insertion, they may not prevent subsequent malposition or vascular perforation. Free aspiration of blood from the catheter, an appropriate pressure trace and the chest x-ray remain the routine methods of confirming the position of a catheter. Contrast studies are a gold standard for catheter position assessment.

Catheterization via the internal jugular vein may result in fewer malpositions than catheterization via the subclavian vein.[6] Generally, catheterization via the left internal jugular vein results in more malposition and vascular perforation than a catheter placed from the right internal jugular vein. This is because the right internal jugular vein runs into the right brachiocephalic vein in a fairly straight course whereas the left internal jugular vein forms a greater bend when it becomes the left brachiocephalic vein. The left internal jugular vein was chosen in this case because there was already an internal jugular cannula on the right-hand side.

Catheter tip migration is a recognized phenomenon following central venous catheterization, occurring to some degree in approximately 17% of all percutaneously introduced catheters.[9] Poor position or aberrant location from catheter tip migration has been shown to occur in up to 6% of catheters.[10] However, only two similar cases of bilateral pleural effusions following central venous catheterization were found in the literature. This is a rare complication that is yet to be satisfactorily explained.

References

1 Campagnutta E, Segatto A, Maesano A, Sopracordevole F, Viscentin MC, Scarabelli C. Bilateral hydrothorax and hydromediastinum after cannulation of the left internal jugular vein. *Minerva Ginecol* 1989; **41**: 479–83

2 Simmons TC, Henderson DR. Bilateral pleural and pericardial effusions because of mediastinal placement of a central venous catheter. *J Parenteral Enteral Nutr* 1991; **15**: 676–9

3 Rudge CJ, Bewick M, McColl I. Hydrothorax after central venous catheterization. *Br Med J* 1973; **3**: 23–5

4 Thomas CJ, Butler CS. Delayed pneumothorax and hydrothorax with central venous catheter migration. *Anaesthesia* 1999; **54**: 987–90

5 Kanno T, Yoshikawa D, Tomioka A, Kamijyo T, Yamada K, Goto F. Hydrothorax: an unexpected complication after laparoscopic myomectomy. *Anaesthesia* 2001; **87**: 507–9

6 Dunbar RD, Mitchell R, Lavine M. Aberrant locations of central venous catheters. *Lancet* 1981; **1**: 711–5

7 Denys BG, Uretsky BF, Reddy PS. Ultrasound-assisted cannulation of the internal jugular vein. A prospective comparison to the external landmark-guided technique. *Circulation* 1993; **87**: 1557–62

8 Gualtieri E, Deppe SA, Sipperly ME, Thompson DR. Subclavian venous catheterization: greater success rate for less experienced operators using ultrasound guidance. *Crit Care Med* 1995; **23**: 692–7

9 Lang-Jensen T, Nielsen R, Sorensen MB, Jacobsen E. Primary and secondary displacement of central venous catheters. *Acta Anaesthesiol Scand* 1980; **24**: 216–8

10 Vazquez RM, Brodski EG. Primary and secondary malposition of silicone central venous catheters. *Acta Anaesthesiol Scand Suppl* 1985; **81**: 22–6

British Journal of Anaesthesia **89** (4): 650–2 (2002)

The stuck central venous catheter: beware of potential hazards

S. Mahadeva, A. Cohen* and M. Bellamy

Intensive Care Unit, St James's Hospital, Beckett Street, Leeds LS9 7TF, UK
**Corresponding author*

Many complications of attempted central venous access have been described, most related to insertion. Larger and stiffer catheters are being used more often for dialysis or massive transfusion. This case report details how one catheter was damaged during the insertion of a second catheter. The problem was discovered when the catheter could not be removed, and was subsequently removed after dissection. The reason for the difficult removal and the likely consequences of excessive force are illustrated.

Br J Anaesth 2002; **89**: 650–2

Keywords: complications, catheter damage; equipment, catheters; monitoring, physiological

Accepted for publication: May 30, 2002

Percutaneous insertion of central venous catheters (CVCs) is routine hospital practice. Complications of this procedure have been well documented. Most arise from problems encountered during insertion (cardiovascular side-effects and bleeding) and during maintenance (infection, thrombosis and mechanical risks).[1] One of the mechanical complications of CVC use is breakage, with the risk that the distal remnant is dislodged as an embolism while a stuck catheter is being removed.[2] We describe an unusual cause of this complication in a fairly common clinical scenario.

Case report

MF, a 48-yr-old female patient with chronic myeloid leukaemia, was admitted with sepsis several weeks after a

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

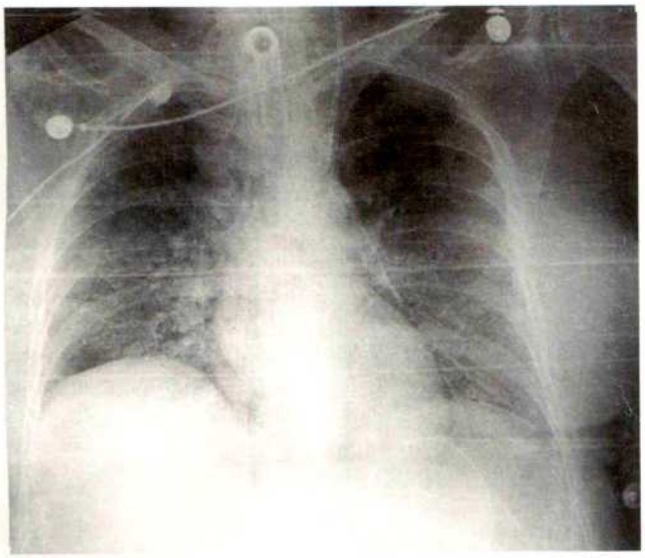


Fig 1 Antero-posterior chest x-ray. The left internal jugular cannula is visible.

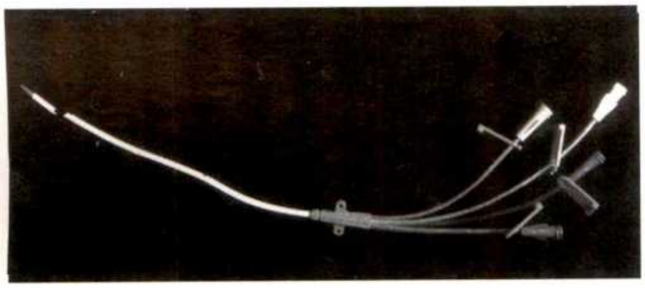


Fig 2 Photograph of left internal jugular catheter after removal. The distal tip became disconnected after secure application of the artery clip during removal.

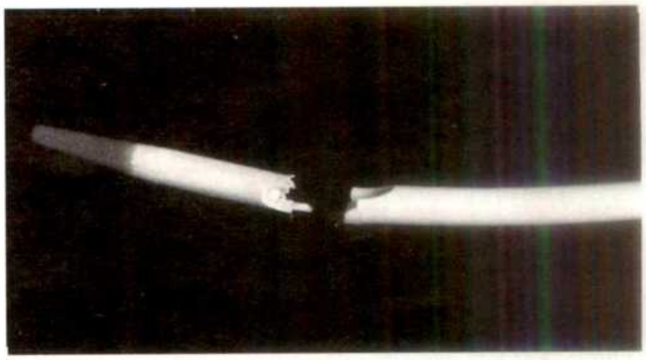


Fig 3 The distal section of left internal jugular catheter. It is possible to see the individual internal lumen (one of four), now fractured.

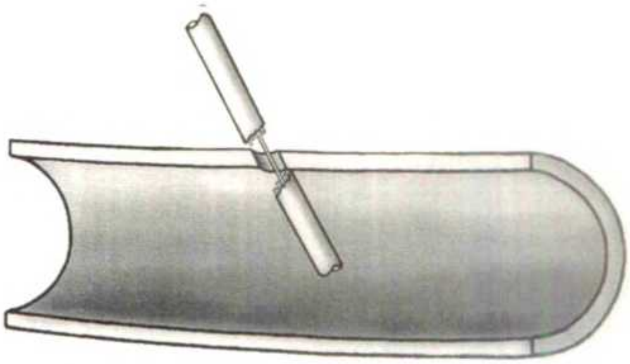


Fig 4 Line drawing representing the internal jugular vein cut longitudinally. It is possible to see the puncture in the vessel wall, the tip of the partially fractured CVC within the lumen and the fracture stuck across the gap. One of the four internal lumens remains intact. Traction on the external part of the line would have resulted in venous embolization.

bone marrow stem cell transplant. Ultrasound scanning of her upper thorax and neck revealed thrombosis in both the right internal jugular and subclavian veins, because of previous catheter insertion for multiple courses of chemotherapy. On the day of admission a 20 cm long, 8.5 Fr, quadruple-lumen CVC (Vygon, Cirencester, UK) was placed in the left internal jugular (LIJ) vein by a Seldinger technique and under ultrasound guidance. The catheter was inserted up to the 15 cm mark, with the remaining proximal portion external to the patient. The position was checked in the usual manner by a chest radiograph (Fig. 1). Seven days later, we decided to replace the existing CVC because of a suspicion of line-related sepsis. Using the same technique, the left subclavian vein was easily cannulated but the guide wire met resistance after advancing several centimetres. A further two attempts were made in a similar manner, with similar results and the procedure was abandoned. Central venous access was obtained without difficulty via the right femoral vein.

Some time later, the nurse caring for the patient reported difficulty removing the LIJ catheter. Resistance was met after 13 cm of the catheter had been withdrawn, with 2 cm of the catheter still within the vascular lumen. Gentle traction was applied to no avail. Close inspection after the entry site had been extended to 1 cm suggested that the catheter had been partially sheared and that complete fracture was imminent. An emergency cut-down procedure was performed along the site of the LIJ vein; the catheter remnant was identified and was found to be connected to the body of the catheter by one remaining intact lumen of the original four. The remnant was secured with an artery clip and was successfully removed (Figs 2 and 3); the incision site was sutured. After removal it was seen that the cause of the catheter being stuck was the ridge caused by the fracture in the external material of the line becoming stuck in the vessel wall on removal (Fig. 4).

No immediate complications arose from this procedure but the patient died with overwhelming sepsis a week later.

Discussion

Shearing or fracturing is a recognized complication of CVC use. One centre reports an incidence of 2.5% over a 5 yr period; however, these incidents were all in neonates.[2] Causes that have been described include shearing by the introducer needle during insertion,[2] high pressure within the catheter caused by bolus infusions,[2] fracturing of the external portion by the patient's body movements (mostly infants),[3] during removal of a stuck catheter (mostly by fibrin sheath formation around the catheter),[4] and weakening of the catheter tip by movements of the tricuspid valve and right ventricular motion[3] or mechanical forces between the clavicle and first rib.[5] In our case, shearing of the LIJ catheter was probably caused by repeated cannulation attempts from the introducer needle in the left subclavian vein, both from the cutting edge of the needle and by blunt trauma from the metallic guide wire. The tip of the LIJ catheter was in the appropriate position for this to have occurred (Fig. 1). In view of this experience, we feel that cannulation of a central vein on the same side as an existing CVC requires caution. When inserting a new CVC the operator should be aware of the position of the tip of an existing CVC in relation to the site of cannulation. Furthermore, resistance to the passage of the introducer needle or guide wire, as we experienced, should be an absolute contraindication to further attempts at cannulation before the other cannula is removed.

Various methods of dealing with a sheared or fractured CVC have also been explored. Most authors advise against applying tension. In contrast, slow gentle traction (up to 36 h!) has been used with some success,[6] but usually in cases with intact CVCs that have become entangled in fibrin sheaths. Cutaneous cut-down followed by distal venotomy to remove stuck catheters that have not fractured completely has been described previously as safe, simple and easily performed at the bedside.[4] Once complete fracture with subsequent embolization has occurred, however, more complicated approaches have been used, including radiological loops, snares and coils, and occasionally surgical exploration as a last resort.[2] Hence, once shearing of a catheter is suspected, we advocate very cautious handling of the CVC. In particular we believe our case highlights that forceful traction on any stuck catheter should be avoided and a cause sought as soon as possible.

In summary, we have described an unusual cause of shearing of a CVC. In critically ill patients, changing a CVC is a common procedure if the existing catheter is possibly infected. Careful handling and immediate bedside attention can prevent more serious sequelae, such as embolization of a fragmented catheter tip. Clinicians should be aware of this previously unreported hazard of CVC use.

References

1 Arenas-Marquez H, Anaya-Prado R, Barrera-Zepeda LM, Gonzalea-Ojeda A. Complications of central venous catheters. *Curr Opin Clin Nutr Metab Care* 2001; **4**: 207–10

2 Trotter C, Carey BE. Tearing and embolisation of percutaneous central venous catheters. *Neonatal Netw* 1998; **17**: 67–71

3 Khilnani P, Toce S, Reddy R. Mechanical complications from very small percutaneous central venous Silastic catheters. *Crit Care Med* 1990; **18**: 1477–8

4 Ng PK, Ault MJ, Fishbein MC. The stuck catheter: a case report. *Mt Sinai J Med* 1997; **64**: 350–2

5 Ramsden WH, Cohen AT, Blanshard KS. Case report: central venous catheter fracture due to compression between clavicle and first rib. *Clin Radiol* 1995; **50**: 59–60

6 Gladman G, Sinha S, Sims DG, Chiswick ML. *Staphylococcus epidermidis* and retention of neonatal percutaneous venous catheters. *Arch Dis Child* 1990; **65**: 234–5

British Journal of Anaesthesia **89** (**4**): 652–5 (2002)

Use of implantable cardioverter defibrillator and anti-arrhythmic agents in a parturient

A. J. Olufolabi[1], G. A. Charlton[2]*, S. A. Allen[3], I. M. Mettam[2] and P. R. Roberts[3]

[1]Department of Anesthesiology, Duke University Medical Center, Durham, NC 27710, USA. [2]Department of Anaesthesia, and [3]Department of Cardiology, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK

**Corresponding author*

We describe a case of a 36-yr-old patient who presented at 14 weeks gestation with multifocal dysrrhythmic episodes. Despite treatment with anti-arrythmic agents and an implantable cardioverter defibrillator (ICD) *in situ*, she continued to experience persistent dysrrhythmic episodes. She was delivered by Caesarean section at 34 weeks under general anaesthesia. We discuss some of the anaesthetic challenges of parturients with ICD devices.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Br J Anaesth 2002; **89**: 652–5

Keywords: anaesthesia, obstetric; complications, arrhythmia; heart, arrhythmia; heart, pacemakers artificial; pregnancy

Accepted for publication: May 12, 2002

The introduction of implantable cardioverter defibrillators (ICDs) into clinical practice in the mid 1980s provided a further option for the treatment of cardiac rhythm disorders. We present a case to show the complexity and limitations of these devices. The case also describes the use of anti-arrhythmic agents in pregnancy and following delivery.

Case report

A 36-yr-old primigravidae (weight 50 kg; height 157 cm) was admitted to the cardiac ward with an unplanned pregnancy at 14 weeks gestation and a history of persistent arrhythmia which required frequent cardioversion. Her past medical history was of surgical correction for double outlet right ventricle, pulmonary stenosis and multiple ventricular septal defects. She had a 4-yr history of episodes of ventricular tachycardia (VT) which were first treated with various anti-arrhythmic agents. An ICD (Mini, Guidant, USA) was implanted 2 yr prior to her pregnancy. In the nine months before she presented, she had numerous (>100 times) ventricular tachycardic episodes despite her anti-arrhythmic treatment with xamoterol 200 mg b.d. and flecanide 50 mg b.d.

She was managed jointly by the Grown Up Congenital Heart (GUCH) Team, electrophysiologists and obstetricians. In the week after presentation, she had further episodes of VT with rates of 194–198 beats min^{-1}. Successful cardioversion treatment restored sinus rhythm but she found each episode distressing. Her ICD was therefore reprogrammed for anti-tachycardia pacing only and disabled from triggering a cardioversion response when it detected a VT rhythm. It would, however, recognize a ventricular fibrillation (VF) signal rate of 240 beat min^{-1} and respond with a 33 J-defibrillation pulse. Her serum flecanide level (240 µg litre^{-1}) was within the normal range of 200–700 µg litre^{-1}. We noted multi-focal beats with intermittent bigeminy but she was otherwise asymptomatic. She had further intermittent episodes of VT, leading to considerable adjustment to her anti-tachycardia pacing setting and anti-arrhythmic medications. Despite this, she continued to have frequent VTs that predominantly were anti-tachycardia paced but which occasionally had a VT greater than 240 beat min^{-1} that required a cardioversion from the device. An initial echocardiogram revealed reduced left ventricular function with a dilated right ventricle and mild tricuspid incompetence.

Although maternal weight was unchanged at 51 kg, an ultrasound scan at 18 weeks revealed a normal foetus of appropriate size for its gestation. The patient refused amniocentesis to determine any potential teratogenic effect of the anti-arrhythmic agents. Maternal serum alpha fetoprotein level was, however, normal at 17 ku litre^{-1}. Low-molecular weight heparin was commenced at 22 weeks gestation because of the increased risk of thromboemboli from the combined hypercoagulable state of pregnancy and reduced cardiac output. Because of persistent episodes of VT, her flecanide dose was increased despite a serum concentration of 350 µg litre^{-1}.

The ICD was tested in the third trimester and confirmed to be in good working order. An echocardiogram revealed no changes to previous results. She developed new and frequent episodes of supraventricular tachycardia (SVT). Because the rate of her SVT was similar to her VT, she received inappropriate shock therapy. Thyroid function tests were checked and were normal. The SVT was terminated pharmacologically with intravenous verapamil. Further adjustments to the ICD detection enhancements were made to discriminate the SVT from the VT so that each rhythm could be appropriately treated. Her arterial pressure was not affected by these episodes and she experienced minimal symptoms. A midwife examined the baby after every SVT/VT episode using a cardiotocogram to ensure that the foetal condition remained satisfactory.

At 30 weeks gestation, and with a maternal weight of 59 kg, she was transferred to a high-dependency unit. A series of abnormal rhythms consisting of VT, SVT, and atrial fibrillation persisted and required further adjustment of her drugs (flecanide, xamoterol, digoxin and magnesium). At 34 weeks gestation, an episode of heart block required reduction of the flecanide and verapamil doses. A decision was made to deliver the baby and three doses of dexamethasone were given to promote foetal lung maturation.

She was transferred to the obstetric theatre. General anaesthesia was planned as the patient refused regional anaesthesia. Experienced obstetric and cardiac anaesthetists, and an electrophysiologist familiar with the ICD functions were present. The device was programmed to 'monitor only' mode by the electrophysiologist for the duration of the Caesarean section. Venous and arterial canulae were placed under local anaesthesia. Following routine anti-reflux prophylaxis, the patient underwent a rapid sequence induction with thiopental 325 mg and succinylcholine 100 mg. Anaesthesia was maintained with 50% oxygen in nitrous oxide and isoflurane 1%. A female 2.1-kg baby was delivered with Apgar scores of 8 and 9 at 1 and 5 min. Oxytocin infusion was started post delivery and intravenous morphine was administered. Blood loss was approximately 600 ml. Postoperative Hb was 10.8 g dl^{-1} (preoperative Hb 11 g dl^{-1}). She had no dysrrhythmic episodes throughout the delivery. A bipolar electrocautery was used intermittently for surgical haemostasis.

After surgery, heparin, digoxin and flecanide were continued and the verapamil dose was reduced. She developed a cough and breathlessness 48 h after delivery. On auscultation, bilateral lung crepitations were heard. An enlarged right ventricle with moderate function was seen by echocardiography. Left ventricular contractility was normal. Her symptoms improved after furosemide. Episodes of recurring SVT occurred on the 6th postpartum day. Digoxin and verapamil treatment was reduced. Varying episodes of bundle branch block occurred that responded to doses flecanide. During her second and third postpartum week, she had numerous cardiac dysrrhythmias that required changes of her anti-arrhythmia drugs. Hypotension accompanied some of these episodes. With episodes of refractory SVT and VT and new evidence of cardiovascular compromise, she underwent cardiac ablation of identified accessory pathways using local anaesthesia with sedation. A new dual chamber ICD (Medtronic 7250) was also inserted. This device is more capable of discriminating between SVT and VT, so that inappropriate therapy is less likely. She also started taking oral amiodarone. Her cardiac rhythm became stable with no further rhythm disturbance. She was discharged after a very long hospital stay (200 days).

Discussion

Cardiac arrhythmia is more frequent during pregnancy. Metabolic and hormonal changes increase cardiac excitability.[1] The patient also has to compensate for the physiological requirements of the developing pregnancy. These changes, which develop in the first trimester before becoming stable in the middle and third trimester, include: increased cardiac output, increased intravascular volume, increased total body water; increased glomerular filtration and renal clearance, increased hepatic enzyme function, and reduced plasma protein.[2] These changes alter the pharmacokinetics and pharmacodynamics of many drugs and consequently their doses. Changes in absorption, volume of distribution, and elimination can make serum levels difficult to predict. Observation of drug serum levels and clinical effects are often required for adequate management.

The risk of teratogenic effects during organogenesis in the first trimester, and effects on growth and development in the second and third trimesters demands caution in the use of medication in pregnancy. Most cardiac drugs appear safe and are classified as category C according to the US Food and Drug Administration, that is, some risk has been found in animals but not in humans.[3] However, phenytoin and amiodarone should be avoided because significant congenital abnormalities are associated with their use.[4]

Most anti-arrhythmic drugs are also safe for nursing mothers. The concentration of the drug in breast milk does not usually exceed maternal plasma concentration, and the amount of drug taken by the baby rarely reaches therapeutic levels.[5] Drugs with a proven record of safe use during pregnancy should be chosen for first line treatment.[4]

The ICD provides both stored and real-time telemetry information that aids the diagnosis of complex rhythm disturbances. It also treats life-threatening cardiac events. Our report describes a limitation of these devices, since single chamber devices may not differentiate between SVTs, VTs and VF, resulting in inappropriate treatment. Only after a dual chamber system was placed were the unstable cardiac rhythms in by our patient correctly identified and appropriately treated.

Hydrocarbon anaesthetic agents such as halothane and enflurane are known to depress the cardiac atrio-ventricular node and thus can initiate or ameliorate dysrrhythmic events.[6] Halothane sensitizes the heart to adrenaline-induced atrial arrhythmias, an effect potentiated by thiopentone.[7] There is, however, no reported evidence of pacing or ICD thresholds affected directly by anaesthetic drugs. Anti-arrhythmic drugs can, however, alter pacing or defibrillation thresholds.[8] This is more relevant in parturients already on antiarrhythmic agents in whom appropriate dosing is already uncertain.

All cardiac devices should be assessed before and after surgery. Pacemaker output failure has been attributed to suxamethonium-induced fasciculations.[9] Although there are previous reports of pacemaker malfunction caused by high voltage intraoperative electrocautery or by magnets,[10 11] modern devices are unlikely to be reprogrammed because specific sequences of information are needed to alter programming. However, electrocautery can directly damage circuitry or the tissue–lead interface, resulting in increased pacing thresholds or inadequate sensing. Bipolar diathermy should therefore be used.

Because of her extreme anxiety, our patient opted for general anaesthesia. General anaesthesia allows use of more invasive monitoring such as a pulmonary artery catheter or transoesophageal echocardiogram. However, there is no clear contraindication to regional anaesthesia. An epidural may be preferable to a subarachnoid block since a more controlled onset of effect is possible. Complex cardiac patients have undergone Caesarean section using regional anaesthesia with good outcome.[12] Regional anaesthesia can give good analgesia and reduce the sympathetic response to surgery. The arrythmogenic and depressant effects of volatile agents are avoided so that perioperative cardiac rhythm disturbances can be reduced.

Better treatment of complex cardiac patients increases the frequency of treatment in pregnancy and challenges all involved in their care, requiring a multidisciplinary approach from cardiologists, obstetricians, anaesthetists, and electrophysiologists.

References

1 Ostrzega E, Mehra A, Widerhorn J, *et al.* Evidence of increased incidence of arrhythmias during pregnancy: a study of 104 pregnant women with symptoms of palpitations, dizziness or syncopy. *J Am Coll Cardiol* 1999; **19**: 125A
2 Sibai BM, Frangieh A. Maternal adaptation to pregnancy. *Curr Opin Obstet Gynecol* 1995; **7**: 420–6
3 *Drugs Facts and Comparisons.* St Louis, MO: Facts and Comparisons, 1997
4 Joglar JA, Page RL. Treatment of cardiac arrhythmias during pregnancy: safety considerations. *Drug Safety* 1999, **20**: 85–94
5 Committee on drugs. Transfer of drugs and other chemicals into human milk. *Pediatrics* 1994, **93**: 137–50
6 Handler CB, Wilton NC, Knight PR. Comparative effects of halothane, enflurane, and isoflurane on atrioventricular conductivity and subsidiary pacemaker function in dogs. *Anesth Analg* 1994; **79**: 455–9
7 Atlee JL, Malkinson CE. Potentiation by thiopental of halothane–epinephrine-induced arrhythmias in dogs *Anesthesiology* 1982; **57**: 285–8
8 Kowey PR, Marinchak RA, Rials SJ, Bharucha DB. Classification and pharmacology of antiarrhythmic drugs. *Am Heart J* 2000, **140**: 12–20
9 Finfer SR. Pacemaker failure on induction of anaesthesia. *Br J Anaesth* 1991; **66**: 509–12
10 Domino KB, Smith TC. Electrocautery-induced reprogramming of a pacemaker using a precordial magnet. *Anesth Analg* 1983, **62** 609–12
11 Bierman PQ, Roche DA, Carlson LG. Abnormal permanent pacemaker inhibition by a magnet. a case study. *Heart Lung* 1993, **22**: 148–50
12 Lockhart EM, Penning DH, Olufolabi AJ, Bell EA, Booth JV, Kern FH. SvO_2 monitoring during spinal anesthesia and cesarean section in a parturient with severe cyanotic congenital heart disease. *Anesthesiology* 1999; **90**: 1213–5

British Journal of Anaesthesia 89 (4) 655–7 (2002)

Anaesthetic management of severe bradycardia during general anaesthesia using temporary cardiac pacing

V. Toprak*, A. Yentur and M. Sakarya

Celal Bayar University, School of Medicine, Department of Anaesthesiology and Reanimation, Manisa, Turkey

**Corresponding author*

There are few reports of management of severe bradycardia with temporary cardiac pacing. We describe a 65-yr-old female patient who developed bradycardia and hypotension on two occasions during general anaesthesia for laryngoscopy. The first episode was treated with atropine, ephedrine, and colloid infusion and the second with a temporary pacemaker and ephedrine.

Br J Anaesth 2002; **89**: 655–7

Keywords: complications, bradycardia; heart, arrhythmia, bradycardia; surgery, laryngoscopy

Accepted for publication: May 30, 2002

Excessive vagal activity, which causes severe bradycardia and hypotension, can be life threatening. The trigger can be painful stimulation of the bronchial, pharyngeal, laryngeal, or oesophageal mucosa.[1] Prompt treatment is needed with urgent restoration of venous return by leg elevation, head down tilt, and i.v. fluids, and the use of anticholinergic and sympathomimetic drugs.[2] A pacemaker should be considered for patients with vasovagal syncope which is frequent and does not respond to medical treatment. The use of a temporary pacemaker for patients who develop bradycardia during general anaesthesia is controversial.[3]

We describe two episodes of severe bradycardia in the same patient during general anaesthesia, the second of which was managed with a pacemaker.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Case report

The patient was a 65-yr-old female who weighed 59 kg. She was admitted to hospital to have direct laryngoscopy and vocal cord biopsy, because of a history of hoarseness. This was to be carried out under general anaesthesia.

She gave a history of a myomectomy under general anaesthesia in 1970, which was uneventful, and asthma for the last 25 yr. Her medications were *N*-acetyl cysteine and an inhaler of fluticasone propionate.

She was given 5 mg diazepam by mouth before going to the operating theatre. She was monitored with non-invasive arterial pressure, electrocardiogram, and pulse oximetry. Her heart rate was 68 beats min^{-1} and arterial pressure 115/78 mm Hg. Anaesthesia was induced with propofol 150 mg, followed by vecuronium 6 mg and fentanyl 200 µg. After the trachea had been intubated with a microlaryngeal tube, her heart rate was 76 beats min^{-1} and arterial pressure was 136/82 mm Hg. Anaesthesia was maintained with 2% sevoflurane in nitrous oxide/oxygen, and the patient was positioned slightly head up to facilitate direct laryngoscopy. Sinus rhythm was present throughout the episode.

Immediately after direct laryngoscopy by the surgeon, the heart rate suddenly decreased to 28 beats min^{-1}. Despite withdrawal of the laryngoscope, bradycardia persisted. Atropine 0.5 mg was given i.v., but the heart rate remained slow and the arterial pressure was 55/28 mm Hg. A further dose of atropine 0.5 mg i.v. had no effect but ephedrine 10 mg i.v. caused the heart rate to increase to 72 beats min^{-1}. Hypotension persisted and was treated with infusion of 500 ml of hydroxyethyl starch. Arterial blood gas and serum electrolyte measurements were normal. After 12 min the patient became cadiovascularly stable. The operation was postponed, and the patient recovered without sequelae. Subsequent cardiac examination was normal.

Six months later the same patient returned for treatment of nasal polyps, by nasal endoscopy. Her hoarseness had resolved with medical therapy. On careful questioning the patient gave a history of attacks of syncope or pre-syncope for 40 yr. A cardiologist suggested a head-up tilt test, and that a temporary pacemaker should be used. Tilting head up to 60° for 45 min[4] had no effect.

For the second operation, she was given diazepam 5 mg by mouth. After applying non-invasive cardiovascular monitors a temporary pacemaker[3] (Dispomedia®) was inserted via the femoral vein to the apex of the right ventricle, and set at 60 beats min^{-1}. Before induction of anaesthesia her heart rate was 66 beats min^{-1} and the arterial pressure was 125/66 mm Hg. Anaesthesia was induced with etomidate 18 mg, followed by vecuronium 6 mg and fentanyl 250 µg. After tracheal intubation, the heart rate decreased. The pacemaker became active and at the same time the arterial pressure was noted to be 76/40 mm Hg. After ephedrine 10 mg i.v., the heart rate was 68 beats min^{-1} and the arterial pressure 106/58 mm Hg. The remainder of the surgery and anaesthesia was uneventful. The pacemaker was withdrawn the day after surgery. The patient recovered completely and left hospital after 3 days.

Discussion

During anaesthesia, changes of heart rate may suggest changes in the depth of anaesthesia, changes in vagal activity, or the effects of drugs or possible hypoxia. Simple vagal reactions usually respond to when the stimulus is stopped. Here, the vagal response was excessive and severe hypotension persisted despite stopping the laryngoscopy.

Tilt-table testing may be useful in the diagnosis of vasovagal syncope, and can guide treatment. However the tilt-table test is positive in only 75% of patients with classic vasovagal syncope. The sensitivities of the various test methods vary widely and they are only 75–80% reproducible, suggesting that they may give an incorrect diagnosis.[3] However, as tilt-table testing is the only investigation that can precipitate a typical attack that can be directly observed, it is taken as the 'gold standard' for the diagnosis of vasovagal syncope.[4]

Clinically, syncope associated with autonomic dysfunction tends to be most frequent early in the day, and is more likely after a period of bed rest, after vigorous exercise, or during drug treatment that can reduce central circulatory volume. Unlike vasovagal faints, these episodes of syncope are not associated with bradycardia, sweating, or marked pallor.[5] Our patient's clinical presentation, and the absence of predisposing factors such diabetes mellitus led us to think she had a vasovagal response rather than autonomic dysfunction.

Treatment of vasovagal syncope with a pacemaker is controversial.[6] Vasovagal syncope can be aborted by dual-chamber pacing, and if syncope does occur, pacing can prolong consciousness.[7] However, in a report of 22 patients with neurocardiogenic syncope, pacing failed to prevent a decrease in arterial pressure during bradycardia caused by tilt testing.[8]

Temporary pacing is most commonly used to treat symptomatic bradycardia for short periods, either before a permanent pacemaker or when the bradycardias is not persistent.[3 6] There are few reports of temporary pacing for general anaesthesia.[9] We suggest that as well as drug treatment, temporary pacing is a useful form of treatment for this condition.

References

1 Hosie L, Wood JP, Thomas AN. Vasovagal syncope and anaesthetic practice. *Eur J Anaesth* 2001; **18**: 554–57

2 Kinsella SM, Tuckey JP. Perioperative bradycardia and asystole: relationship to vasovagal syncope and the Bezold-Jarish reflex. *Br J Anaesth* 2001; **86**: 859–68

3 Sheldon R. Role of pacing in the treatment of vasovagal syncope. *Am J Cardiol* 1999; **84**: 26–36

4 Kenny RA, Ingram A, Bayliss J, Sutton R. Head-up tilt: a useful test for investigating unexplained syncope. *Lancet* 1986; **1**: 1352–5

5 Mark AL. Cardiopulmonary baroreflexes in humans. In: Shepherd JI, Abboud FM, eds. *Handbook of Physiology, Section 2: The Cardiovascular System*, Vol. III. Bethesda, MD: American Physiological Society, 1983; 795–813

6 Haye S, David L. Pacemakers. In: Topol Eric J, ed. *Textbook of Cardiovascular Medicine*. Philadelphia: Lippincott-Raven Publishers, 1998; 1879–1911

7 Glikson M, Espinoza RE Hayes DL. Expanding indications for permanent pacemakers. *Ann Intern Med* 1995; **123**: 443–51

8 Sra JS, Jazayeri MR, Avitall B, *et al* Comparison of cardiac pacing with drug therapy in the treatment of neurocardiogenic (vasovagal) syncope with bradycardia or asystole. *N Engl J Med* 1993; **328**· 1085

9 Fuentes Rodriguez R, Sebastianes Marfil MC, Mato Ponce M, Morales Guerrero J, Torres Morera LM Preoperative prophylactic pacemakers. apropos of their indication in a disputed case. *Rev Esp Anestesiol Reanim* 2001, **48**· 38–41

British Journal of Anaesthesia **89** (4): 658–63 (2002)

Correspondence

Interdisciplinary collaboration in anaesthesia research

Editor—Interdisciplinary collaboration is an important aspect of contemporary academic medicine. It is recognized as essential to allow translation of advances made in the laboratory to advances in clinical practice.[1 2] The extent to which researchers are collaborating with experts outside their field is a key indicator of research practice patterns, and may have implications for the likely impact of such research within the parent specialty and in other fields of medicine. We noticed that there is no information concerning the nature or extent of collaboration occurring in anaesthesia research, the manner in which this may have changed during the recent evolution of our specialty, or the differences that exist between countries. We therefore performed a manual survey of papers describing original research, published in four major English-language anaesthesia journals by sampling one year from each of the past five decades.

Journals surveyed were *Anaesthesia*, *Anesthesia and Analgesia*, *Anesthesiology* and the *British Journal of Anaesthesia*; 3001 articles were included. We found that the number of authors per paper, the number of countries represented and the proportion of studies which are multicentre and international have increased progressively during the past 50 yr ($P<0.05$, Chi-square test for trend) (Table 1). There have been steady increases in the proportion of papers that are the product of collaboration with clinical and non-clinical specialists from disciplines other than anaesthesia, and in the variety of such disciplines. The two countries with the greatest share of publications, the US and the UK, differ greatly in their collaborative practices. In the year 2000, 49.2% of US papers involved collaboration of two or more disciplines, whereas 30.4% of UK papers involved multidisciplinary collaboration. Our data may understate this difference as many US investigators hold joint appointments with basic science departments but for the purpose of this analysis they were considered to be anaesthetists only. Among the five countries publishing the most papers in 2000 (USA, UK, Japan, Germany and France), there were no differences in the tendency to collaborate between clinical and non-clinical disciplines (data not shown). Overall a trend was evident; whereas in 1950 research papers published by a sole author were common, in subsequent decades these became increasingly rare. Collaboration with additional anaesthetists from within the same centre increased, followed by collaboration with anaesthetists from other centres and from other countries, and collaboration with specialists from other medical and scientific disciplines. The year 2000 was the first year of those surveyed in which specialists from outside medicine and science were represented (e.g. economics, business administration).

The influence of multi-disciplinary involvement in anaesthesia research cannot be measured by a survey of this kind although we submit that this increase represents a healthy trend for the specialty. A positive impact of multi-disciplinary collaboration in research has been demonstrated in primary care.[3] Academic emergency medicine physicians have produced a consensus statement on research collaboration which includes recommendations on how this may be fostered within and particularly outside their specialty.[4] The last 20 yr have been notable for landmark advances in several biological sciences including molecular biology and genetics. To harness these developments for the advance of anaesthesia, it will be necessary to establish and maintain collaborative networks with experts in these fields.[2] Several factors tend to hamper this, however, including: the structural organization of academic medical institutions;[2] grant application procedures that reward only the principle investigator; difficulties among clinicians and basic scientists in recognizing merit in each others work;[5] and potential for disagreements over authorship.[6]

We limited this survey to four major American and UK anaesthesia journals. It is possible that distinct trends in collaboration may be more demonstrable in subspecialty journals or in basic science journals. The relative contribution of participants within a collaborative network cannot be assessed from the current method of author listing, (although alternative methods have been suggested),[6] nor can the impact of these experts on the advance of anaesthesia be quantified. Nevertheless, experts from a burgeoning variety of disciplines have become involved in anaesthesia research; it is probable that they have considerably influenced its scope and impact.

L. G. Kevin[1]
A. J. Cunningham[2]
[1]*Milwaukee*, WI, USA
[2]*Dublin, Ireland*

1 Stein EK, Jessop DJ. Thoughts on interdisciplinary research (editorial). *J Clin Epidemiol* 1988; **41**: 813–5
2 Pober JS, Neuhauser CS, Pober JM. Obstacles facing translational research in academic medical centres. *FASEB J* 2001; **15**: 2303–13
3 Scherger JE, Rucker L, Morrison EH, Cygan RW, Hubbell FA. The primary care specialists working together: a model of success in an academic environment. *Acad Med* 2000; **75**: 693–8
4 Lewis LM, Callaham ML, Kellermann AL, Marx JA, White DJ. Collaboration in emergency medicine research: a consensus statement. *Acad Emerg Med* 1998; **5**: 152–6
5 Freireic EJ. Who took the clinical out of clinical research? Mouse versus man. *Clin Cancer Res* 1997; **3**: 2711–22

Table 1 Survey results. Note Multicentre excludes international studies. *Excludes *Anesthesia & Analgesia* (in 1990 professional disciplines of authors were inconsistently stated)

	1950	1960	1970	1980	1990	2000
Authors (mean (SE))	1.7 (0.07)	2.1 (0.09)	2.6 (0.06)	3.2 (0.07)	4.0 (0.07)	4.9 (0.06)
Sole author papers (%)	52.4	38.4	19.8	9.6	3.6	1.4
Countries (*n*)	10	12	24	26	28	47
Multicentre (%)	4.1	6.5	5.8	10.7	16.3	17.1
International (%)	0	0	1.2	2.5	5.0	11.1
Disciplines (*n*)	3	7	22	37	38*	53
Multidisciplinary (%)	2.7	18.4	30.3	43.5	33.6*	47

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

6 Smith R. Authorship: time for a paradigm shift? *BMJ* 1997; **314**. 992

Risk of accidental extubation with disposable tonsillectomy instruments

Editor—As a result of the increased prevalence of nvCJD within the UK population, there has been concern about the theoretical risk of transfer of prions during tonsillectomy and adenoidectomy. Disposable instruments were widely introduced in 2001, but concerns regarding the safety of these instruments led to the return to reusable instruments in England. In Scotland, the use of disposable equipment remains mandatory. Although the main concern regarding disposable tonsillectomy equipment is an increase in the postoperative haemorrhage rate,[1] we noted an increased incidence of herniation of RAE tubes through the gap in the blade of the Boyle Davis gag (Fig. 1), risking inadvertent extubation. This could endanger the security of the airway if the gag is moved or adjusted during surgery, and has been previously reported with non-disposable equipment[2–4]

We tested various combinations of RAE tubes and blade sizes with disposable and non-disposable sets and found that herniation was more common with the disposable sets. This is most likely to occur in children aged 4–8 yr, due to the similarity between the tube sizes and the width of the gap in the tongue blades used in this age group.

Different sizes of Boyle Davis tongue blades (sizes 2.5–4.5 inches, Rocketmedical) and RAE tubes (4.5–7.0 mm) were assessed. Blade sizes 2.5 and 3.0 inches were found to have the same size of gap (5 mm anteriorly, 6 mm posteriorly), and blade sizes 3.5, 4.0 and 4.5 inches also have the same gap width (5 mm anteriorly, 7 mm posteriorly). We repeated the study using non-disposable instruments.

The results show that RAE tube sizes 4.5, 5.0 and 5.5 mm are the most likely to herniate with any size of tongue blade. With larger RAE tubes, herniation was less likely as the gap in the tongue blade is smaller than the external diameter of the tube. When the study was repeated with the non-disposable sets it was also found that herniation was less likely to occur. This is because the gap size is smaller, and the area of the blade next to the gap is bevelled to accommodate the tube. It should also be noted that RAE tubes are more malleable at body temperature and this may increase the risk of herniation.

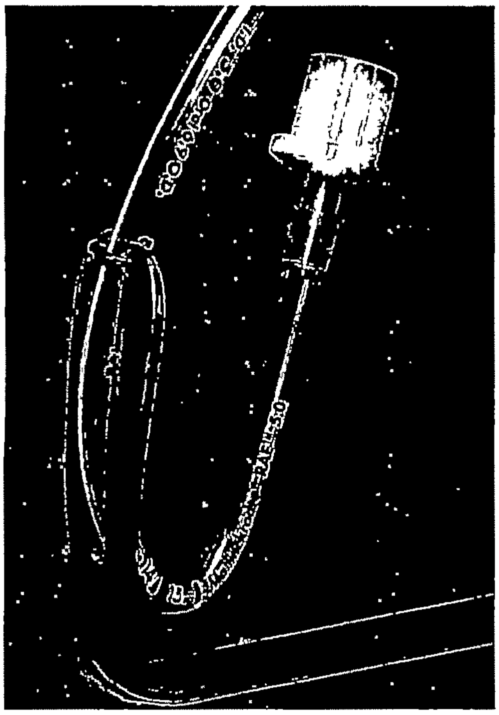


Fig 1 RAE tube herniating through gap in the blade of a Boyle Davis gag

Whilst the risk described above may vary with different equipment manufacturers, anaesthetists and otolaryngologists should be alert to the possibility of the tracheal tube being inadvertently displaced during adenotonsillectomy. This problem should also be considered by companies manufacturing disposable tonsillectomy sets.

D. M. Wynne
J. N. Marshall
Glasgow, UK

1 Complications post tonsillectomy and adenoidectomy. *Memorandum of BAO-HNS* 9 November 2001
2 Shirley PJ, Kulkari V, Frost N. A problem with the Boyle Davis gag following difficult intubation. *Anaesthesia* 1994; **49** 551–2
3 Oliver JJ, Rao J. Modification of the Doughty blade for the Boyle Davis gag. *Anaesthesia* 1994, **49**. 89
4 Sen AK, Gupta B. Herniation of RAE tube through gap Boyle Davis gag. *Anaesth Intensive Care* 1990; **18**: 77–8

Airway management in the emergency department

Editor—The debate on airway management in the emergency department continues unabated.[1–5] One of the major difficulties surrounding this area is the definition of complications in this setting, and the lack of consistency in published studies which makes comparisons difficult and open to misinterpretation.

Berry[2] misquoted from a preliminary abstract of the Scottish Rapid Sequence Intubation (RSI) study,[6] by suggesting that 25% of RSI patients were intubated without an anaesthetic drug The abstract actually states that 123 patients were intubated without the need for anaesthetic drugs and these were excluded from the reported group of patients that actually underwent a formal RSI. It may be of interest to note that this two year prospective study of nearly 1631 patients (of whom 735 had a rapid sequence intubation) is now complete and awaiting publication.[7]

The study shows that emergency physicians perform rapid sequence intubation on patients who are more physiologically unstable (91.8% *vs* 86.1%, $P = 0.027$), and on a higher proportion of patients within 15 min of arrival in the emergency department (32.6% *vs* 11.3%, $P < 0.0001$) than do anaesthetists, with no statistically significant difference in complication rates (12.7% *vs* 8.7%, $P = 0.1$). Anaesthetists achieve better laryngoscopic views (94.0% *vs* 89.3% $P = 0.039$) and have higher first attempt success rates (91.8% *vs* 83.9% $P = 0.001$), but the overall success rate is identical for the two specialties.[7,8]

Berry[2] suggests that increasing the role of emergency physicians in airway management would 'blur the boundary between the two departments'. We believe this would be of undoubted benefit to the critically ill patient by improving collaboration between the two specialties, along with training and standard setting in this critically important subject. The realistic suggestions for progress proposed by Nolan and Clancy[1,9] are welcome and should be pursued in a careful and monitored fashion.

C. A. Graham[1]
D. Beard[2]
D. W. McKeown[2]
[1]*Glasgow, UK*
[2]*Edinburgh, UK*

1 Nolan J, Clancy M. Airway management in the emergency department *Br J Anaesth* 2002, **88**: 9–11
2 Berry J. Airway management in the emergency department *Br J Anaesth* 2002; **88**: 876–7
3 Davies G, Lockey D. Airway management in the emergency department *Br J Anaesth* 2002; **88**: 877
4 Kuehne J. Airway management in the emergency department. *Br J Anaesth* 2002; **88**: 877–8
5 Adams M, Bandara L. Airway management in the emergency department. *Br J Anaesth* 2002; **88**: 878
6 Beale JP, Graham CA, Thakore SB, *et al.* Endotracheal intubation in the accident and emergency department. *J Accid Emerg Med* 2000; **17**: 439
7 Graham CA, Beard D, Oglesby AJ, *et al.* Rapid sequence intubation in Scottish urban emergency departments *Emerg Med J* 2002 (In press)
8 Graham CA, Beard D, Oglesby A, *et al.* Rapid sequence intubation in Scottish urban emergency departments *Emerg Med J* 2002; **19**: 279–80
9 Nolan J, Clancy M. Airway management in the emergency department. *Br J Anaesth* 2002; **88**: 878–9

Prediction of neurological outcome following outside hospital cardio-respiratory arrest

Editor—We read with interest the case report on neurological outcome prediction in a cardiorespiratory arrest survivor by Goh and colleagues.[1] We would like to report a similar incident which occurred in our hospital

A 45-yr-old male collapsed suddenly in the street. The person who witnessed the collapse alerted the London Ambulance Services within 10 min. When the paramedics arrived 8 min later, there was no respiratory effort and no palpable pulse. The ECG monitor showed ventricular fibrillation. Sinus rhythm was restored after the first DC shock of 200 joules. The carotid pulse became palpable and the heart rate was 106 beats min^{-1}. Arterial pressure was 102/53 mm Hg. The patient started to breathe but remained unconscious with a Glasgow coma scale of 3. The cervical spine was stabilized with a hard collar. Tracheal intubation was attempted by the paramedics but failed. The airway was maintained with a Guedel airway and jaw thrust. The respiratory rate was 5–6 bpm. Oxygen 15 litres was administered via facemask with a reservoir bag. An oxygen saturation of 96% was achieved at the scene and the patient was transferred to our hospital.

On arrival in the accident and emergency department, the patient was making spontaneous respiratory effort and his oxygen saturation was 95%. Air entry was poor bilaterally with coarse basal crepitations. The heart rate was 90 beats min^{-1} with an arterial pressure of 100/50 mm Hg. The Glasgow coma scale improved to 5/15. He was moving all four limbs to painful stimulation. The pupillary size was 3 mm bilaterally and sluggishly reactive to light. Following preoxygenation and rapid sequence induction, the trachea was intubated without any complications. Sedation was maintained with a propofol infusion. A bolus of atracurium was administered to facilitate intermittent positive pressure ventilation. A 12-lead ECG showed sinus rhythm with non-specific ST segment abnormality. An urgent CT scan of head did not show any abnormality Cervical spine x-rays were normal. Chest x-ray revealed consolidation of the right middle and lower lobes secondary to aspiration. The patient was transferred to the intensive care unit (ITU) for further management.

During his stay in ITU, the patient's clinical condition was complicated by convulsions and sepsis The first episode of convulsions occurred 7 h after the cardiac arrest. This initially responded to phenytoin 1.35 g and Diazemuls 10 mg. Phenytoin 300 mg was continued once daily. Further seizure activity required treatment with Diazemuls and sodium valproate. Sedation was maintained with infusions of propofol, midazolam and alfentanil. He remained stable cardiovascularly, initially requiring epinephrine 0.6 μg kg^{-1} min^{-1}, which was later weaned and substituted by dobutamine 7.5 μg kg^{-1} min^{-1}. An echocardiogram showed a normal size left ventricle with reasonable systolic function. The right ventricle was dilated with poor systolic function and the right atrium was mildly dilated. EEG revealed epileptic activity correlating with the clinical signs. The troponin T level on day 3 was 0.08 μg litre^{-1}. Pulmonary angiogram performed on day 7 showed no evidence of pulmonary embolism. Percutaneous tracheostomy was performed on day 10. Despite anticonvulsant therapy, the patient continued to have seizures and adopted a decorticate posture. In view of this, the poor prognosis was discussed with the family and a decision was made not to resuscitate in the event of cardiac arrest.

However, from day 11, the patient made a dramatic improvement in neurological function. He responded appropriately to conversation and began obeying commands The decision not to resuscitate was therefore cancelled. The GCS gradually improved to 15/15. Respiratory support was weaned. By day 14, the patient was able to sit up in bed but could not maintain his balance. The seizure activity gradually decreased and he demonstrated full power in both arms and legs. Sensation in both limbs was normal and he had no contractures. On day 20, he was able to mobilize in the ITU using a Zimmer frame, but still continued to have difficulty in coordinating movements The tracheostomy was sealed with occlusive dressing. He could eat a normal diet. He was then referred to the rehabilitation unit for further management. He made a complete physical and neurological recovery by day 29, including past and recent memory. He is due to be discharged home soon. He is booked for an elective coronary angiogram

We believe that our patient suffered cerebral hypoxia during cardiorespiratory arrest possibly secondary to a coronary event. This may have caused a period of ventricular tachycardia and led to no cerebral perfusion for up to 18 min He did not have any CPR during this period. Despite restoring cardiac output after the first DC shock of 200 joules, he remained unconscious. Duration of anoxia and postanoxic coma are considered prognostic indicators. Our patient adopted a decorticate posture and experienced generalized seizures. He had no history of epilepsy. In the ICU, the patient continued to have clinical and EEG evidence of epileptic activity, which was difficult to control. The patient also developed generalized myoclonic jerks. Similar to the case report by Goh and colleagues,[1] our patient too, in spite of these poor prognostic features, made a good neurological recovery It is possible that there was some on-going systemic perfusion during the collapse, which was followed by ventricular fibrillation.

Conventional clinical and EEG assessment of neurological recovery from cerebral hypoxia after cardiac arrest can be misleading. With the current paucity of ITU beds, it is difficult to determine time periods in resuscitation policies. Both Goh's patient and our own have shown that unexpected improvement can occur. Therefore the decision 'not for resuscitation' needs to be reviewed in the light of unexpected neurological improvement.

R. Srikiran
G. Menon
Croydon, UK

1 Goh WC, Heath PD, Ellis SJ, Oakley PA Neurological outcome prediction in a cardiorespiratory arrest survivor. *Br J Anaesth* 2002, **88**· 719–22

An audit of Robertshaw double lumen tube placement using the fibreoptic bronchoscope

Editor—An editorial by Pennefather and Russell[1] added to the continuing debate about confirming the location of double lumen tubes with a fibreoptic instrument Papers were quoted which found a primary malplacement rate varying between 39%[2] and 83%,[3] with one[4] reporting critical malposition in at least 13% The need for further checks throughout surgery was also suggested.[1] Most of the evidence used to support these conclusions was based on the use of plastic tubes and only one paper, that by Hurford and colleagues,[5] involved any of the genuine Robertshaw pattern tubes (then made by Leyland Medical, now by Phoenix Medical Ltd. of Preston, Lancashire), which continue to be widely used in many parts of the world However, only 21% of their 70 Robertshaw intubations were confirmed with fibreoptic bronchoscopy, whilst 7% (no doubt with some overlap) were checked in the course of surgery. This department uses Robertshaw tubes extensively but with varying methods of placement, and in the current climate it was felt necessary to audit the location of a series of conventionally placed tubes by inspection with a fibreoptic bronchoscope

Consecutive conventional Robertshaw double lumen intubations carried out by one of us (AS) were checked by a second consultant thoracic anaesthetist using a fibreoptic bronchoscope Cases where it was difficult to obtain a satisfactory clinical location were excluded, as were those where a suitable fibreoptic bronchoscope or bronchoscopist were not available. The findings from surgical bronchoscopy were available in most instances. The induction sequence included an antisialogogue (atropine 600 µg). Invariably, intubation of the dependent lung was attempted with the largest Robertshaw tube that would negotiate the larynx. The location sequence relied mainly upon visual inspection, estimating relative compliance and listening for leaks. In a few troublesome cases, final checks were made with the aid of a pressure/volume loop trace [2] Bronchial cuffs were primed and inflated with saline, the precise amount required being accurately adjusted. Fixation employed sleek over a Guedel airway. When the patient was turned into the lateral position, the degree of head flexion used during intubation was maintained since it is known that flexion and extension may advance or withdraw the tip respectively.[6]

Fifty adults were included in the audit—36 males and 14 females. There were 35 major thoracotomies, seven video-assisted thoracoscopies, five open lung biopsies and three other procedures. The Robertshaw tubes used were as follows left, 17 large, five medium and three small, and right, 16 large, eight medium and one small (a 50/50 split). In the 14 females 10 medium and four small tubes were used Thirty-three males accepted large tubes and three required medium—all right sided In one of these the large tube stuck at the larynx and the other two failed to advance sufficiently into the bronchial tree

The single fibreoptic bronchoscope check was made as soon as practicable after commencement of surgery. The tracheal and bronchial sides were checked primarily to ensure that both main and upper lobe bronchi were free of obstruction The extent to which the tube departed from the best possible (that is, optimal) position having regard to the anatomy was also noted. We grouped the observations into four categories

(i) Optimal or near-optimal. In the case of a left-sided tube 'near optimal' is defined as up to 1 cm from the perfect position, consistent with unobstructed airways and a clear view of the main carina and sub-carina With the right-sided tube, there is little scope for variation and the two terms become synonymous.

(ii) Sub-optimal. This can only apply to a left-sided tube and indicates a situation where it is more than 1 cm from the best possible position but with both the main and sub-carina still visible and no obstruction to the right main or left upper lobe bronchi.

(iii) Misplaced (but satisfactory) Here the tube is out of position but the lungs are safely isolated and there is a reasonable passage into the appropriate main and upper lobe bronchi.

(iv) Unsatisfactory. Potentially dangerous, bad enough to require re-positioning.

The tube positions noted on fibreoptic bronchoscope checking were as follows

(i) 42 (84%) were optimal or near-optimal

(ii) 6 (12%) were sub-optimal but satisfactory.

(iii) 2 (4%) were malplaced but satisfactory.

(iv) No tube was designated unsatisfactory or required re-positioning

None of the 50 investigations gave rise to any clinical problem that could be attributed to the position of the tube Of the two instances of malplacement one was a medium left tube in a female scheduled for right video-assisted thoracoscopy. It proved impossible to detect the position of the left upper lobe orifice on clinical grounds because, as it turned out, it was completely stenosed. The tube had deliberately been pulled back as far as possible, consistent with satisfactory lung isolation and the main carina was partly obscured, although there was a good passage into the right main bronchus. The second was a large right tube in a 56 kg, 173 cm male which behaved normally in all respects but was, in fact, wedged in the right main bronchus above, and clear of, the right upper lobe orifice. The left main bronchus was not obstructed and there was no clinical indication to replace the tube.

Fifty-two patients were omitted from the audit This was mainly because of the absence of a suitable fibreoptic bronchoscope or bronchoscopist, but positioning problems were a factor in nine cases One wholly and two partially tracheal, right upper lobe orifice locations were noted by an experienced surgeon at bronchoscopy in patients destined for right-sided tubes. These apart, the failure to obtain completely satisfactory clinical location in 102 consecutive patients was 6%—in line with other comparable series.[7 8] The nature of the location problems made it unlikely that this figure could have been improved upon by direct visualization. Our main findings were as follows

(i) Where placement of a Robertshaw tube, without the aid of a fibreoptic bronchoscope, was satisfactory on clinical grounds, this was confirmed in at least 96% of cases upon direct visual inspection—indeed, there was no instance of critical malposition

(ii) Where a Robertshaw tube had been carefully placed and firmly fixed, its position was unlikely to alter Our single fibreoptic bronchoscope check was made *after* positioning the patient The timing was random and eventually it would have detected that tubes were being displaced during surgery, even if that was not clinically apparent.

There can be no doubt that the fibreoptic bronchoscope is a useful tool. However, for an experienced anaesthetist, this audit has not shown it to be essential; indeed the instrument provides objective support for the contention by Conacher and colleagues[8] that the design and materials of the Robertshaw tube contribute to safe deployment by conventional means. The ability to place a Robertshaw tube blind may be vital where, for example, a suitable flexible bronchoscope is not available or there is heavy bleeding into the bronchial tree.

A. H. Seymour
L. Lynch
Birmingham, UK

Acknowledgement: We gratefully acknowledge the help of Dr Brendan O'Connor, consultant anaesthetist, in conducting this audit.

Editor—Thank you for the opportunity to reply to Seymour and Lynch who conclude from an audit of patients receiving red rubber Robertshaw (Phoenix) double lumen endobronchial tubes (DLEBT) that the use of a fibreoptic bronchoscope is not essential for these patients. In our opinion, neither this audit nor the literature they quote support this conclusion.

Seymour and Lynch audited the blind placement of red rubber tubes in 102 consecutive patients. They bronchoscoped 50 patients, in one patient undergoing left lung anaesthesia, an occluded left upper lobe bronchus was detected. Nine of 52 patients omitted from this study were excluded because of difficulty placing the DLEBT blindly. In three of these nine patients there was a tracheal origin to a right upper lobe or right upper lobe segmental bronchus. No details of the location problems experienced in the remaining six patients are given but a fibreoptic bronchoscope would have facilitated the accurate placement of an alternative DLEBT/ bronchial blocker if optimal placement of the DLEBT in use could not be achieved. As discussed in our editorial, the variability in tracheobronchial anatomy is central to any discussion on placement of DLEBT and cannot be dismissed.[1] It is difficult to comment on the incidence of significant DLEBT malplacement during this audit because of the large number of patients excluded. It can be concluded that using a fibreoptic bronchoscope in all audited patients would have provided clinically useful information and/or aided the accurate placement of an appropriate tube to provide one lung ventilation (OLV) in at least 10% of these patients.

Seymour and Lynch quote a paper by Hurford and colleagues[5] auditing the blind placement of DLEBT by residents working in their department. Seventy of their patients received a red rubber Robertshaw DLEBT (Leyland). Fibreoptic bronchoscopy was never performed on 55 of these 70 patients. The DLEBT was repositioned in 13 of the 15 patients in whom fibreoptic bronchoscopy was performed after initial blind placement of the DLEBT. Thus although 19% of all Robertshaw tubes were repositioned as a result of bronchoscopy following initial blind placement, the tube was repositioned in 87% of those patients in whom the initial blind placement was checked with a fibreoptic bronchoscope.

Seymour and Lynch quote Conacher and colleagues,[8] who prospectively analysed the blind placement of 100 red rubber Robertshaw DLEBTs (Leyland) without the use of a fibreoptic bronchoscope. Reasonable surgical conditions and oxygenation were achieved in 90% of patients. In 11% of patients, difficulty was experienced in ventilating the contralateral lung; this was presumed to be due to bronchial cuff herniation. Upper lobe bronchus blocking by the tube was detected in 8% of patients

We agree with Seymour and Lynch that the ability to place a DLEBT blindly is a useful skill and that red rubber tubes of the original Robertshaw design are best suited for blind placement. We teach our registrars to place a variety of DLEBTs blindly. However, we require our registrars to then check and recheck the position of all blindly placed DLEBTs with a fibreoptic bronchoscope. Most registrars need no further convincing that a fibreoptic bronchoscope should be used in all patients.

As discussed in our editorial, the routine use of fibreoptic bronchoscope facilitates the detection of anatomical and pathological variation in the structure of the major airways, thus enabling the choice and placement of an appropriate tube to provide OLV.[1]

We are of the opinion that the audit by Seymour and Lynch and the literature they quote adds further support to the arguments for the routine use of fibreoptic bronchoscope in all patients undergoing OLV.

S. H. Pennefather
G. N. Russell
Liverpool, UK

1 Pennefather SH, Russell GN. Placement of double lumen tubes—time to shed new light on an old problem. *Br J Anaesth* 2000, **84**: 308–10

2 Bardoczky GI, Levarlet M, Engelman E, Defrancquen P Continuous spirometry for detection of double-lumen endobronchial tube displacement. *Br J Anaesth* 1993; **70**: 499–502

3 Alliaume B, Coddens J, Deloof T. Reliability of auscultation in positioning of double-lumen endobronchial tubes *Can J Anaesth* 1992; **39**: 687–90

4 Klein U, Karzai W, Bloos F, *et al.* Role of fiberoptic bronchoscopy in conjunction with the use of double-lumen tubes for thoracic anesthesia: a prospective study. *Anesthesiology* 1998; **88**: 346–50

5 Hurford WE, Alfille PH. A quality improvement study of the placement and complications of double-lumen endobronchial tubes *J Cardiothorac Vasc Anesth* 1993; **7**: 517–20

6 Saito S, Dohi S, Naito H. Alteration of double-lumen endobronchial tube position by flexion and extension of the neck *Anesthesiology* 1985, **62**: 696–7

7 Zerdin GL, Short DH, Ryder GH. An assessment of the Robertshaw double-lumen tube. *Br J Anaesth* 1965; **37**: 858–60

8 Conacher ID, Herrema IH, Batchelor AM. Robertshaw double lumen tubes: a reappraisal thirty years on. *Anaesth Intensive Care* 1994; **22**: 179–83

Somebody else's nervous system

Editor—The editorial by Fettes and Wildsmith is informative and interesting.[1] I would like to highlight a particular problem with the combined spinal epidural technique (CSE). In the conventional spinal anaesthetic procedure, the needle is supported by the interspinous ligament and ligamentum flavum, even if it is introduced through an introducer, adding stability to the needle. In CSE, the very fine spinal needle is only held by the tissues of the epidural space, dura and arachnoid membranes. There is a risk of needle movement while attaching the syringe and injecting the local anaesthetic, increasing the risk of nerve damage. Thus, it is possible for the needle to come into contact with a nerve towards the end of the injection, after it has been bathed with local anaesthetic, without eliciting paraesthesia.

R. Shankar
Bedford, UK

Editor—We would like to thank Dr Shankar for his kind comments, and the journal for the opportunity to reply. Dr Shankar raises another concern about the use of the combined spinal epidural technique (CSE) which, although not our primary subject, does give rise to some concern. We agree that, because of the lack of ligamentous support, there is greater scope for the spinal needle to move during CSE. However, it should always be remembered that this possibility still exists with the standard single needle spinal. The main point which we wished to make in our editorial,[1] was that any instrumentation of the vertebral canal should be conducted with the utmost care.

Dr Shankar's second point is interesting and may be at least partly valid. Local anaesthetics penetrate the nerve rootlets very quickly in the subarachnoid space, where there are no nerve sheaths, and movement at the end of injection could well lead to damage here without contemporary symptoms. However, injection of local anaesthetic takes only a few seconds, so whether the drug would have time to affect the spinal cord itself is another question. Thus Dr Shankar's point is unlikely to be relevant to the cases described by Dr Reynolds,[2] which triggered our editorial. All seven patients felt pain on insertion of the spinal needle, and six had evidence of spinal cord damage on subsequent magnetic resonance imaging scan.

P. D. W. Fettes
J. A. W. Wildsmith
Dundee, UK

1 Fettes PDW, Wildsmith JAW. Somebody else's nervous system. *Br J Anaesth* 2002; **88**: 760–3
2 Reynolds F. Damage to the conus medullaris following spinal anaesthesia. *Anaesthesia* 2001; **56**: 238–47

British Journal of Anaesthesia 89 (4): 664–8 (2002)

Book Reviews

Clinical Anesthesia Practice R. R. Kirby, N. Gravenstein, E B. Lobato and J. S. Gravenstein (editors). Published by Saunders, Philadelphia. Pp. 1704; indexed; illustrated. Price £98.00. ISBN 0-7216-8566-8.

The first edition of this book was published in 1994 Its stated aim was to provide clinically useful information for trainees and specialists. This was achieved by adopting a 'question and answer' format, very much like a case discussion. The aim and format for the present edition are the same. The editors and over 100 contributors, the majority of them from Florida, have endeavoured to compile a total of 76 chapters in 10 different sections. This is a challenging project that attempts to cover the whole breadth of anaesthesia practice, except intensive care medicine, in an unconventional format.

The first section, quite suitably, is 'Toward a Safer Practice'. This section covers essential elements of pre-anaesthetic evaluation, quality assurance, critical incident management, medico-legal issues, and many other relevant topics. The chapters keep the reader 'engaged' in the safety aspects of anaesthetic practice, which have gained importance in recent years. The chapters on quality assurance and medico-legal aspects reflect American practice, but the information provides valuable insight into various issues in these areas. Section 2 is on preoperative consultations. The chapters deal with evaluation and preoperative management of patients with pre-existing medical problems. While all the important aspects of cardiovascular, respiratory and renal diseases are well covered, I was disappointed by the lack of information on the liver, and on endocrine and connective tissue diseases in this section. Section 3 deals with equipment and has all the relevant details on modern anaesthetic machines. The chapter on airway devices is excellent. However, I was unable to find enough information on the Mapleson classification of breathing circuits and their clinical application. Section 4 deals with most currently used monitoring devices, but a keen reader might fail to find enough details on the relevant aspects of physics. Also, a comprehensive review of on-line analysis of inhalation anaesthetic agents and its clinical application is missing.

I liked Section 5 which deals with clinically relevant anatomy. The chapters on the anatomy of the airway, spine, autonomic nervous system, and vascular access are interesting to read and make the clinical relevance of the knowledge of anatomy instantly apparent. Section 6 covers most of the essential aspects of the pharmacology of anaesthetic agents. The chapter on drug interactions gives important interactions in a tabular form which are instantly available for quick reference However, information on other important and commonly used drugs such as inotropes, antihypertensive agents, other vasoactive drugs, anti-arrhythmic agents, and drugs acting on airway is lacking in this section. Section 7 presents the physiology and pathophysiology of different systems This section presents complex physiological phenomenon in an easily understandable manner. The approach of combining basic physiology with pathophysiology and interactions with pharmacological agents, draws the knowledge from different areas and crystallizes it into a clinically relevant format.

Section 8 comprehensively deals with problems related to hazardous environments. Section 9 covers the problems related to certain patient groups (e.g pregnancy, extremes of age) and to certain specialized surgical procedures. I enjoyed going through theses chapters which have plenty of useful information and detail. However, in this section, I could not find enough information on certain important and/or commonly encountered procedures, for example, anaesthesia for phaeochromocytoma, eye surgery, electroconvulsive therapy, and cardioversion. Section 10 is on transplantation and covers all the relevant transplant procedures in adequate detail.

Overall, I found this book easy to read and follow with its appropriate and extensive use of tables, illustrations, flow-charts, photographs, and references. The content of each chapter is up-to-date, and it reflects good, safe practice throughout. Residents and trainees will find plenty of useful information in this 'question and answer' format, which will help them to recognize the clinical importance of a particular topic. Also, this approach imparts essential knowledge from different areas of clinical practice in a problem-solving manner. However, because of the inherent nature of organizing a book in this way, trainees may find that the information on one particular area can be scattered throughout it. Lack of enough information on some key topics, such as anaesthesia for an obese patient and others that I have already mentioned, does not render this book the first choice for preparing for examinations. For a busy practitioner, however, the book provides up-to-date information on most aspects of anaesthesia practice in an easy-to-read format. I am sure it will find a place on their bookshelves for quick reference. However, they will have to rely on other texts for certain topics related to high-dependency care, unusual medical problems, and complex pain management issues.

R. P. Mahajan
Nottingham, UK

Anesthesia for the Cardiac Patient. Christopher A. Troianos (editor). Published by Mosby, Inc , St Louis. Pp. 656; indexed; illustrated. Price £75.00. ISBN 0-323-00874-7.

Since the publication of two sets of guidelines—the first in 1996 by the American College of Cardiologists and American Heart Association; and the second in 1997 by the American College of Physicians—the perioperative management of patients with cardiovascular disease has been the subject of innumerable publications. In *Anesthesia for the Cardiac Patient*, Christopher Troianos and his 30 contributing authors have attempted to bring together, in one volume, a comprehensive review of the management of patients with cardiovascular disease undergoing cardiac *and* non-cardiac surgery.

The book comprises 22 chapters divided into four parts: perioperative care of the cardiac patient, anaesthetic management of cardiac disease, specific cardiothoracic surgical procedures, and non-cardiac surgical settings. The book is extensively referenced and the overall layout is excellent, as is the quality of the numerous figures and tables. Each chapter concludes with a list of key learning points and key references. The chapters on preoperative assessment and risk evaluation, intraoperative monitoring, and perioperative transoesophageal echocardiography (TOE) provide excellent reviews, although the latter lacks a concise list of clinical indications and is really only applicable to cardiac surgery. Curiously, no mention is made of potassium channel openers, statins, or anticoagulants in the cardiovascular medication chapter, and the discussions of postoperative care, cardiothoracic intensive care and pain relief are, to my mind, a little short. The section dealing with the anaesthetic management of patients with coronary, valvular, electrophysiological, and

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

congenital heart disease is both concise and comprehensive. The repetition of discussion of preoperative risk assessment in the chapters on coronary artery disease and ambulatory surgery is a minor annoyance, as is the omission of any discussion on detecting and managing perioperative pacing problems. The section on cardiac surgery begins with an overview of cardiopulmonary bypass, and moves on to minimally invasive surgery, thoracic aortic surgery, and transplantation. The detailed description of ventricular assist devices has to be balanced against the absence of any detailed discussion of valve surgery. The final section deals with vascular, thoracic and ambulatory surgery, trauma, neurosurgery, and obstetrics.

From the outset, *Anesthesia for the Cardiac Patient* is an ambitious project, particularly when one considers that the 'standard' cardiac anaesthesia texts are all considerably longer. The discussion of TOE billing codes and the omission of any reference to the European System for Cardiac Operative Risk Evaluation (EuroSCORE), suggests that this is very much a volume targeted at North America. It is perhaps unfortunate that neither the Foreword nor the Preface gives any clue as to who the intended target readership might be. Having now read the book, I still remain unsure. For trainees and generalists there is perhaps too much detail—evidenced by discussions of minimally invasive cardiac surgery and ventricular assist devices. For the cardiothoracic specialist, there is too little detail. For my money (and for the trainee preparing for specialty examinations), the standard cardiac tomes, Benumof's *Anesthesia for Thoracic Surgery*, Jonathan Mark's *Atlas of Cardiovascular Monitoring*, and Bobbie Jean Sweitzer's *Handbook of Preoperative Assessment and Management*, remain unsurpassed.

J. E. Arrowsmith
Cambridge, UK

The Year in Interventional Cardiology: 2002. H. D. White, P. J. de Feijter, B. Meier, A. Colombo, A. P. Banning and R. Schrader. Published by Clinical Publishing Services Ltd, Oxford. Pp. 360; indexed; illustrated. Price £49.50. ISBN 0-9537339-7-1.

Interventional cardiology is a rapidly developing field with a strong emphasis on evidence-based treatment. Each year sees the publication of many clinical studies designed to further define the role of both percutaneous interventions and pharmacological therapy in the management of coronary artery disease.

The Year in Interventional Cardiology: 2002 is the first edition in what we are told will be a regular series. Its purpose is to bring the reader up-to-date in one volume by presenting the important clinical studies published between 2000 and 2001 Key areas are reviewed with several internationally renowned experts having contributed to this edition. This book is not meant to be an introduction to interventional cardiology and a basic understanding of important principles and previous studies is necessary to follow the text. It is primarily aimed at interventional cardiologists and would be useful for those in training or in research.

The book is divided into six main sections, which are the pharmacological management of acute coronary syndromes, percutaneous coronary intervention in acute coronary syndromes, stents, restenosis, cardiac imaging outside the catheter laboratory, and contrast agents. The background, results and interpretation of these studies are well presented with important emphasis on clinical application of the results. Where relevant, useful tables, graphs and figures are clearly presented.

The consistent application of this structured format presents the reader with information in a very logical and precise manner. However, it is very difficult to get a grasp of the overall subject as the development of previous ideas and reference to past studies is often scant.

Percutaneous interventions in acute coronary syndromes both with and without ST segment elevation are well covered, with clear discussions comparing the use of conservative and interventional strategies. The adjuvant use of glycoprotein 2b/3a inhibitors, low molecular heparins, and thienopyridines is addressed. The chapters on the development of restenosis and its treatment, with particular emphasis on brachytherapy, are well covered. The use of drug-eluting stents is briefly mentioned in stent design and coating, but there is little information about more recent developments in their ability to limit restenosis

Developments in carotid and renal artery stenting are well summarized, but there is no mention of the use of covered stents in the treatment of aortic dissections or aneurysms. The last few chapters of the book discuss the emerging role of new imaging modalities such as 3D echocardiography, MRI, and electron beam computerized tomography in guiding clinical practice.

The chapters are well structured with the information presented in a clear and concise manner. Important topics are covered in detail and well indexed to be useful sources of reference. The conclusions at the end of each chapter provide the reader with a clear summary and unanswered questions are identified.

We feel that this book goes a long way towards achieving its objective in covering the latest developments in interventional cardiology. The contributors have done an excellent job in summarizing the extensive literature to produce a useful collection of key clinical studies, which are well presented. However, in the rapidly moving field of interventional cardiology, the next volume is already awaited.

S. Aziz and R. H. Stables
Liverpool, UK

Cardiogenic Shock: Diagnosis and Treatment. David Hasai, Peter B. Berger, Alexander Battler and David R. Holmes Jr (editors). Published by Human Press, New Jersey. Pp. 370; indexed, illustrated. Price US$135. ISBN 1-58829-025-5.

Every time that I manage to get a patient who is in cardiogenic shock onto cardiopulmonary bypass without inducing complete cardiovascular collapse, I give myself a metaphorical pat on the back. Cardiogenic shock is one of the most challenging conditions to manage as an anaesthetist or intensive care specialist and any insight into its pathophysiology or management is most welcome. This book sets out to provide such knowledge.

Reading the list of authors and their affiliations left me icy cold. Although there was a sprinkling from Europe and New Zealand, the authors were predominately from Israel and the USA and I was concerned that information the book contained might not be relevant to European practice. In addition, I could only spot one anaesthetist in a list of 41 authors who, apart from the odd surgeon, were overwhelmingly cardiologists. Therefore, I was also uncertain whether the book would have any relevance to anaesthetic or intensive care practice. However, my feelings towards the book thawed with each successive chapter that I read. In the end, there was only one chapter, which discussed transportation of patients in cardiogenic shock, that was purely a description of US practice and even it was interesting to read. Regrettably, my second reservation was born out as the book contains little to directly enhance the knowledge and experience of an anaesthetist. Any benefit of reading this book for anaesthetists is to gain a deeper understanding of the cardiological and surgical approaches to cardiogenic shock.

Cardiogenic shock has many causes and there are many different approaches to its management. To its credit, the book tries to present an evidence base to the information provided. However, because of its nature, there has been little robust scientific investigation of many of the areas covered by this book and practice is often governed by clinical experience. There are seven parts to the book that start with clinical practice and pathophysiology, and finish with transportation of patients, future mechanical assist devices and alternatives to the human heart, as well as some, as yet esoteric, molecular biological approaches to shock. In between, parts to explore include· shock complicating acute coronary syndrome; contemporary management of this syndrome; mechanical complications of acute myocardial infarction; shock related to valvular heart disease; and shock related to other conditions including myocarditis, pericardial and congenital heart diseases. The chapters are generally well written but vary in style of presentation according to author and topic Many are also well illustrated and all are well referenced.

Although much of the information is not of direct practical value to an anaesthetist, the book provides a broad overview of the subject. The one chapter on operative strategies that does contain advice about anaesthesia was far too much a description of an institution's practice and not enough of a review of the subject. To be fair, there is not a lot of evidence to review on anaesthesia for cardiogenic shock. What little there was came with some sound pieces of advice. For instance, what is important is not the specific anaesthetic agents one chooses but how one uses them! Unsurprisingly, as a cardiac anaesthetist, I found the surgical chapters such as those on post-infarct ventricular septal defects and papillary muscle rupture, most enlightening. Valuable reviews of mechanical assist and heart replacement devices, which are rapidly changing areas of innovation, are also provided.

There is not much to motivate a non-cardiac anaesthetist to wade their way through 21 chapters on cardiogenic shock However, a cardiac anaesthetist or a general intensive care specialist who is involved in the management of cardiological complications, will gain much insight from reading some, or all, of this book.

R P. Alston
Edinburgh, UK

Practical Pain Management (third edition). C. David Tollison, John R. Satterthwaite and Joseph W. Tollison (editors). Published by Lippincott Williams & Wilkins, Philadelphia. Pp. 800; indexed; illustrated. Price $129.00. ISBN 0-7817-3160-7.

There are eight sections to this book: foundations, diagnostics, therapeutic modalities, pharmacologic interventions, the treatment of selected pain disorders, cancer pain and medico-legal issues and selected topics—a total of 800 pages written by 81 authors.

This book is a mixture of the good and bad, some chapters being well thought out and clearly written, and some not. The book is divided into various sections, although sometimes the logic of this division is strange. I can highly commend the section involving the treatment of selected pain disorders. Here we seem to have experts in their particular fields giving up-to-date clear information. The same cannot be said for the preceding three chapter sections; approximately 300 pages, which I am sure, could be condensed with no loss of information and with increased clarity to 100 pages Some chapters are almost unreferenced, the value of which with our current evidence-based approach, at least in the UK, is highly questionable. This book is very American with almost no attempt to disguise the fact and the question must be asked, is it really aimed at the worldwide market? In the preface, the editors state that they enjoyed the opportunity to interact with clinicians from across the world. Only two authors were from outside the United States, one of them being from Canada. The sections of the book dealing with managed care and the Social Security Disability System are not strictly relevant to Europeans, although it does well for us to know what to expect for the future.

Overall there are some sections in the book that are very well written, and if specific topics are sought, this book is excellent. Read as a whole, the repetition and, in some cases, scientific questionability of the writing, become very irritating and counter-productive to concentration. It is not a book I would wholeheartedly recommend, although reference to it would be valuable.

J Richardson
Bradford, UK

Manual of Pain Management (second edition) C. A. Warfield and H. J. Fausett (editors). Published by Lippincott Williams & Wilkins, Philadelphia. Pp. 407; indexed; illustrated Price US$59 95 ISBN 0-7817-2313-2.

This is the second edition of a successful text on pain management, some 10 yr having passed since the first edition was published In essence, this is an excellent introduction into the field of pain medicine, covering acute, chronic, and cancer pain. The authors and editors have successfully managed to cover this expanding specialty within one single volume. The first edition was a success, and this revised edition will be widely used. The aim of the text appears to be the same: the use of self-contained, and usually short, chapters that can be used by the reader with ease. As with all multi-author books, there is some variability in the approach to each chapter, but in general the book successfully reaches its aim of presenting pain medicine in small easily digested chapters. The text is split into four sections: (i) Understanding pain; (ii) Pain by anatomic location; (iii) Common painful syndromes; and (iv) Pain management. New chapters include. interstitial cystitis; injection therapies; treating patients with addictions; paediatric, elderly, and HIV/AIDS pain; and legal issues.

The whole tone of this book is very much set by the editors' introduction. This in itself is worth reading because it highlights the rapid advances made in North America to establish pain as 'The fifth vital sign' The editors draw our attention in their introduction to the work of the Joint Commission on Accreditation of Health Care Organisations (JCAHO) and the American Pain Society towards this aim. The introduction also makes special note of the wide range of educational opportunities in pain medicine afforded by the internet, and gives websites for the American Medical Association, the American Pain Society, and JCAHO. The editors intended that this new edition of the *Manual of Pain Management* should provide the support needed to successfully meet the challenge of providing good pain management care in the new millennium. My impression is that they have been successful.

The book is presented as blocks of text with black and white diagrams and figures. Initially, some readers might find this less than up-to-date in presentation, but with the short design of each chapter and regular use of the text, the layout does become acceptable.

In the first section 'Understanding pain', the history, pathophysiology, endogenous opioids, neurotransmitters, nerve conduction studies, and the psychological evaluation of pain are covered. This section therefore aims to be an overview of pain, its pathophysiology and its assessment. Each chapter is short and easily readable: the first chapter on 'History of pain relief' is impressive, especially as it has such a forward-looking flavour to it. The second section 'Pain by anatomic location', addresses pain in terms of its symptom, e.g. 'headache' or 'ear pain'. For the practising clinician this is invaluable. Again the chapters are concise, well written, and offer valuable advice to the clinician in the pain clinic. The third section 'Common painful syndromes', addresses pain in a more general fashion: 'arthritis', 'cancer pain', 'phantom limb pain', 'acute pain management', 'trauma' etc. This section would also be invaluable for the practising clinician. The fourth section 'Pain management', addresses the pharmacology of pain with chapters on analgesic therapies, and has sections on injection therapies, physical measures, behavioural therapies, surgery, and general considerations on pain management. Various chapters in this section will be useful to different readers, but this reviewer found the overview on systemic analgesics to be very attractive especially with its use of patient examples. The two chapters on surgical approaches to pain are also excellent; and the section comprising four chapters on general considerations in pain management are useful. For example, the final chapter on 'Legal aspects of pain management' contains much valuable advice.

It is likely that the second edition of *Manual of Pain Management* will make an important contribution to the development of pain medicine in the next few years. The editors have been successful in improving an established textbook and making the second edition relevant to current practice. I believe it would be useful as an introduction to this area, and also to practising clinicians looking for a handy reference text to use in the clinic.

I. Power
Edinburgh, UK

Atlas of Common Pain Syndromes. S. W. Waldman. Published by W. B. Saunders, Philadelphia. Pp. 315; indexed; illustrated. Price £63.00. ISBN 0-7216-7577-8.

The commonest problem seen in most pain clinics in the United Kingdom is low back pain, with or without leg pain. I was surprised therefore to find that neither back pain nor low back pain appear in the index of this book. Rather than common pain syndromes, this book deals with pain syndromes to which a name can be given, and usually describes a nerve block or some other invasive treatment that the author thinks appropriate for that diagnosis. For each diagnosis, the author gives a brief description of the clinical syndrome, the signs and symptoms, tests that can be done, the differential diagnosis, treatment, complications and 'clinical pearls'. No evidence is given for any of the material and there are no references. The word 'Atlas' in the title is rather misleading as many of the illustrations merely show a drawing of a patient in pain, sometimes accompanied by anatomical drawings that only show the area of the pain and add nothing to the understanding of the condition.

The whole approach of the book is simplistic and pays no attention to the dramatic advances in our understanding of chronic pain and its management in the past 30 yr. The contribution of neurophysiology and pharmacology is almost totally ignored. The role of clinical psychology would appear to be almost non-existent. For almost every condition the author recommends a nerve block or some other type of invasive treatment. The concept that patients with chronic pain have a complex biopsychosocial problem is not part of the approach in this book. It seems that the author assumes that each patient has a diagnosable and understandable cause for their pain. By addressing the supposed underlying cause, the patient will be cured. Sadly, this is far from the reality. Many patients coming to pain clinics cannot be given a meaningful diagnosis, only a descriptive one, which really only tells the patient what they know already, for example, low back pain, chronic daily headache, or phantom pain. The insights gained from the neurosciences have shown how complex many chronic pain syndromes are. Neural plasticity involving changes at the receptor, axon, spinal cord and brain occur in many conditions. It is now recognized that these changes and dysfunction within the nervous system are contributory factors in many pain syndromes. This has made many older treatments such as nerve blocks, especially destructive blocks, seem less relevant to most pain clinicians. The evidence for the effectiveness of many of these procedures is lacking, and there are many reports of patients being made worse by them.

An example of the shortcomings might be in the chapter on phantom limb pain. The illustration shows a man sitting on a pavement, holding a begging bowl, with a sign saying 'homeless lost job Vietnam vet'. There is an anatomical drawing of a pelvis showing the sciatic nerve. The author briefly discusses the genesis of phantom pain, mentions the spinal cord, but no reference is made of other recent developments such as cortical remapping. He states that people born with congenitally absent limbs do not suffer phantom pain. This old notion has now been disproved. Pre-emptive analgesia is recommended, even though studies have shown that it is not effective. Other pain problems suffered by amputees such as stump pain and back pain are not mentioned. The author lists various forms of treatment, and states that they have been shown to be useful in the palliation of phantom limb pain. No evidence or references are given for this optimistic statement.

Another example might be the chapter on atypical facial pain which concentrates on the diagnoses which must be excluded, and states 'the major pitfall when caring for patients thought to be suffering from atypical facial pain is the failure to accurately diagnose underlying pathology responsible for the patient's pain'. This seems to ignore the fact that most patients coming to pain clinics with this diagnosis have been thoroughly investigated and the problem lies in their management not in the diagnosis. The treatment focuses on drugs and physical modalities such as oral orthotic devices and physical therapy. Nerve blocks are said to be of possible value. Psychological help receives only a brief mention.

Pain medicine has come a long way since 1965 when Melzack and Wall proposed the Gate Control Theory. The complexity of the problem at a physiological, pharmacological and psychological level can be daunting, but we have to address this complexity. I do not feel that this book helps in this endeavour.

W. A. Macrae
Dundee, UK

Heal the Pain, Comfort the Spirit. Dorene O'Hara. Published by University of Pennsylvania Press, Philadelphia. Pp. 237; indexed; illustrated. Price £14.00. ISBN 0-8122-1795-0.

My impression of this book suggested that it would be of a spiritual nature, rather than pain related, due to its cover of blue and white fluffy clouds. In *Heal the Pain, Comfort the Spirit* Professor Dorene O'Hara examines the issues of the pain experience: the biology of painful injury, how it effects our minds and bodies, and the medical and physical therapies available. The emphasis of this book is on the overwhelming nature of chronic pain, and it is the author's belief that 'comforting' the mind will 'heal' the body. Hence, it has a strong bias towards the psychological aspects of pain and its management.

For the trainee anaesthetist or nurse practitioner interested in pain management, this book would be a useful reference providing an overview of chronic pain. This book also gives valuable insight into the pain process, detailing self-help strategies and the various methods of treatment available for the pain sufferer.

The book consists of 10 chapters, with sections on sources (agencies), additional notes, and an extensive bibliography (20 pages each). The text is easy to read and well referenced. Throughout, the author provides many examples of >pain patients, as well as examining contributions made by other clinical professionals and researchers to their management.

Chapters one and eight, 'How we think about pain' and 'Stress, psychology and pain in the bodymind', focus on the psychological issues of pain. The author examines the pain experiences learned from childhood and the initial response to injury, through to the cognitive behavioural mechanisms of chronic pain. The second chapter, 'The treatment of pain: history and analysis', is short, giving a brief overview of the evolution of pain, its treatment, and how multidisciplinary pain clinics were first established.

The third chapter, 'Pain as self-defence', explores the biological and stress responses to painful stimuli or injury. The author discusses the various pain theories and the effects of pain on our circadian rhythms. 'The vicious circle' expands further on the biological process and the social implications of managing chronic pain.

Chapter five, 'Pain complaints', explains the importance of assessment and diagnosis Pain clinics offer patient management plans focusing on psychological techniques and alternative therapies In some cases, traditional treatments are recommended as in 'just make it go away'. This chapter briefly describes the different pharmacological methods (NSAIDs, antidepressants, nerve blocks), for the management of acute and chronic pain. Chapters seven and nine, 'It hurts so good' and 'Integrative medicine', discuss the various physical or alternative therapies available for use in treating pain.

In chapter 10 'Putting it all together' the author presents a selection of cases; some patients have been illustrated earlier in the text and they are used to demonstrate how a multidisciplinary clinic works. Case histories include post-herpetic neuralgia, low back and abdominal pains.

In summary, this book is a resource for background information about chronic pain. Health professionals interested in working in this field would require more in-depth literature, as the reviewer learnt nothing new. Many chapters appeared similar and repetitive due to the psychological bias. Yet, for the pain sufferer, this is a pleasant self-help book.

F. Ion
Liverpool, UK

British Journal of Anaesthesia 89 (4): 669 (2002)

Erratum

High-dose tinzaparin in pregnancy and the need for urgent delivery (BJA 2002; 89: 331–4)

The corresponding author of this article was incorrectly marked as G. R. Lyons whereas it should have been S. K. Backe.

The publishers apologize for this error

Dr Backe would also like to point out that his present address is now:

Wansbeck General Hospital, Woodhorn Lane, Ashington NE63 9JJ, UK

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

British Journal of Anaesthesia 89 (4): 670–81P (2002)

BJA

ABSTRACTS

Proceedings of the Anaesthetic Research Society Meeting

University of Wales College of Medicine, Cardiff

July 11–12, 2002

*(The name of the author presenting the paper is shown in bold type. *Indicates non-member. All authors have certified that, where appropriate, studies have been conducted with the approval of the relevant Human Ethics Committee or Animal Experimental Review Committee.)*

VERBAL PRESENTATIONS

Comparison of two Macintosh laryngoscope blades

T. Asai, S. Matsumoto* and K. Shingu*

Department of Anaesthesiology, Kansai Medical University, Moriguchi City, Osaka, 570-8507, Japan

Sir Robert Macintosh stated that 'the precise shape or curve of the blade does not seem to matter much'[1] and that 'there is so little difference in the performances of the various blades'.[2] Nevertheless, two major types of Macintosh laryngoscope blades (standard and 'English' type (E type)) are available: compared with the standard blade, the length of the E type blade is longer, its curve is more continuous across the entire length of the blade, and the height of the blade flange is shorter. In addition, the flange of the E type blade continues close to the blade tip, whereas the flange of the standard blade ends more abruptly and further away from the tip. We felt that, compared with the standard blade, the E type blade might provide a better glottic view, and thus assessed the ease of laryngoscopy between the two Macintosh blades.

We compared the two types of laryngoscope blades manufactured by Welch Allyn (NY, USA) in 300 patients, 116 males and 184 females, mean age 49 (range: 18–82) yr, mean height 160 (130–180) cm and mean weight 58 (33–94) kg. In a random cross-over design, after induction of general anaesthesia and neuromuscular blockade, the two blades were inserted in turn in each patient. The view of the glottis at laryngoscopy was graded according to Cormack and Lehane for each blade. The McNemar test was used to compare the incidence of difficult laryngoscopy (grade 3 or 4) between the two blades. $P<0.05$ was considered significant.

There was no difference in the view of the glottis between the two laryngoscope blades in 220 of 300 patients, whereas there was a difference in the remaining 80 patients. Of these 80 patients, the view was better for the E type in 63 patients whereas the standard was better in the remaining 17 patients. Laryngoscopy was difficult (grade 3 or 4) at least for one laryngoscope blade in 42 of 300 patients (14%). Of these 42 patients, there was no difference in the grade between the two blades in 14 patients (33%), the view was better for the E type in 25 patients (60%), and the standard blade better in the remaining three patients (7%). The McNemar test showed that in patients in whom the laryngoscopy was difficult (grade 3 or 4), the view of the glottis was significantly better for the E type blade than for the standard blade ($P<0.001$). The 95% confidence interval for the possibility of the type E being better than the standard blade in patients with difficult laryngoscopy was 45–74%.

We have found that the type E laryngoscope blade provided a better glottic view significantly more frequently than the standard blade in patients in whom laryngoscopy was unexpectedly difficult.

Keywords: intubation tracheal, difficult, equipment, laryngoscopes

References

1 Macintosh RR *Lancet* 1943; i: 205
2 Macintosh RR. *Lancet* 1944; i: 485

Effect of repeated exposure on the incidence of adverse airway events during brief nasal inhalations of anaesthetics

A. R. Wilkes, N. Raj* and J. E Hall*

Department of Anaesthetics and Intensive Care Medicine, University of Wales College of Medicine, Cardiff CF14 4XN, UK

We investigated whether the different levels of humidification provided by various breathing system filters affected the incidence of adverse airway events during brief nasal inhalations of volatile anaesthetics. Twelve volunteers who had airways that responded adversely to 2.0 MAC desflurane were recruited. Each volunteer came to the laboratory on four separate occasions, once for each of the four anaesthetics: sevoflurane, halothane, isoflurane and desflurane. The volunteer breathed nasally through a facemask attached to one of three different filters and, after 3 min, inhaled a single breath of 0.5, 1.0 or 2.0 MAC anaesthetic, in air. The volunteer then breathed air only until the expired MAC level was zero, before the next breath of anaesthetic. When all three levels of the anaesthetic had been inhaled once with each filter (nine breaths), each combination of anaesthetic level and filter was repeated twice more, each time in a different order. Although the filter used, and hence humidification level, was not a significant explanatory variable,[1] further analysis has shown that repeated exposure was (Table 1).

Repeated exposure to anaesthetics led to reduced irritancy to the airways even when the expired level of the anaesthetic was zero between breaths. This may be due to desensitization of, or the

© The Board of Management and Trustees of the British Journal of Anaesthesia

Table 1 Number of breaths during which an adverse airway event (reduction or cessation of inspiratory or expiratory flow or coughing) occurred. Summed for all humidification levels. Results from GLIM (Generalized Linear Interactive Modelling) logistic regression analysis anaesthetic, $P<0.001$, anaesthetic level, $P<0.001$; humidification, $P=0.09$, 'repeat', $P<0.001$

Anaesthetic	MAC level	Incidence of adverse airway events (n=36)			Total (n=108)
		First exposure	Second exposure	Third exposure	
Sevoflurane	0.5	4	1	2	7
	1.0	4	2	3	9
	2.0	8	7	5	20
Halothane	0.5	6	2	3	11
	1.0	6	5	3	14
	2.0	19	17	12	48
Isoflurane	0.5	5	3	2	10
	1.0	6	6	4	16
	2.0	24	19	13	56
Desflurane	0.5	6	5	5	16
	1.0	14	11	9	34
	2.0	34	28	27	89

result of very low dose effect of anaesthetic on, the chemoreceptors in the upper airways.

Acknowledgement: We gratefully acknowledge the funding provided by the Association of Anaesthetists of Great Britain and Ireland.

Keywords: anaesthetic techniques, inhalation; potency, anaesthetic, tolerance

Reference

1 Wilkes AR, Raj N, Hall JE *Eur J Anaesthesiol* 2002; **19**: A157

Comparison of the peak forces that can be exerted by multiple-use and single-use bougies in vitro

A. R. Wilkes, I Hodzovic* and I P Latto*

Department of Anaesthetics and Intensive Care Medicine, University of Wales College of Medicine, Cardiff CF14 4XN, UK

The multiple-use gum elastic bougie is widely used as an aid during difficult intubation.[1] However, it is difficult to ensure that the multiple-use bougie is cleaned adequately before re-use.[2] A single-use bougie is also available, but is less widely used. The single-use bougie appears to be stiffer than the multiple-use version. This might cause an increase in the risk of trauma to tissue during placement. The peak forces that could be exerted by the tips of the two types of bougies were therefore investigated in the laboratory.

Five samples of both multiple-use (Eschmann Healthcare Tracheal Tube Introducer) and single-use bougies (Portex Tracheal Tube Introducer) were each held at four different positions (10, 20, 30 and 40 cm from the tip) and pressed three times onto a disc attached to a force transducer with a resolution of 0.1 N (Mecmesin PFI200N). A depression in the disc prevented the tip of the bougie from slipping as the bougie bent. The peak force was recorded for each test and the results from the two types of bougie were compared for each position using the Mann–Whitney U test. A P-value of <0.01 was considered significant because of the multiple comparisons.

Table 2 Peak force (N) that could be exerted when pressing the multiple-use and single-use bougies against the force transducer when held at different distances

Distance held from tip (cm)	Median peak force (N) [IQR]		Mann–Whitney U test P-value
	Multiple-use	Single-use	
10	4.4 [3.7–5.4]	10.8 [10.1–11.5]	<0.0001
20	1.7 [1.5–2.2]	4.8 [4.1–5.0]	<0.0001
30	0.9 [0.7–1.2]	2.3 [2.1–2.4]	<0.0001
40	0.4 [0.4–0.5]	1.2 [1.2–1.3]	<0.0001

The peak force that could be exerted on the disc at every position by the single-use bougies was two to three times greater than that which could be exerted by the multiple-use bougies (Table 2). The peak force decreased with increasing distance from the tip.

As the force exerted by the tip of the bougie is over a relatively small area, the peak pressure that could be applied to the tissue is considerable. This study suggests that the single-use bougie is more likely to cause trauma to tissue during placement. A recent *in vitro* study demonstrated that successful placement of the single-use bougie was much less likely than the multiple-use bougie.[3] Although the contamination risk may be less, using the single-use bougie in place of the multiple-use bougie may cause an increase in patient morbidity.

Keywords: equipment, gum elastic bougie; intubation tracheal

References

1 Latto IP, Stacey M, Mecklenburgh JS, *et al Anaesthesia* 2002; **57**: 379–84
2 Cupitt JM. *Anaesthesia* 2000; **55**: 466–8
3 Annamaneni R, Hodzovic I, Wilkes AR, *et al Eur J Anaesthesiol* 2002; **19**: A141

A clinical appraisal of the Bonfils Intubating Fibrescope

M. Halligan*, B. Weldon* and P. Charters

University Hospital Aintree, Longmoor Lane, Liverpool, UK

The Bonfils Intubating Fibrescope is a rigid stylet-type laryngoscope. It enables a tracheal tube to be advanced beyond the vocal cords under direct vision. Our aim was to confirm its use as safe, reliable and atraumatic.

Sixteen patients requiring tracheal intubation for routine ENT surgery were recruited. All were ASA I or II and aged 17–64 yr. Exclusion criteria were a risk of aspirating gastric contents and inter-incisor distance <3 cm. One anaesthetist performed all the intubations. Patients were given midazolam 2 mg intravenously then preoxygenated for 3 min. Next fentanyl 1 $\mu g\ kg^{-1}$, propofol 2.5 $mg\ kg^{-1}$ and atracurium 0.5 $mg\ kg^{-1}$ were administered and after a further 3 min, intubation attempted. If after a further 2 min there was no success an assistant performed a sustained jaw thrust. Three minutes was the maximum time allowed for a successful intubation and this was the primary outcome measure Secondary outcomes included time taken (including need for jaw thrust) and evidence of trauma as assessed by post intubation conventional direct laryngoscopy. Subjective difficulty was scored with rating scale (0–10) with relative contribution of patient versus instrument/user factors.

Intubation was achieved in all cases. Average time taken was 69 (range 34–180) s Jaw thrust was used in 2/16. There was no evidence of traumatic intubation. The Graphical Representation of Instrumentation Difficulty (GRID) is a novel method for

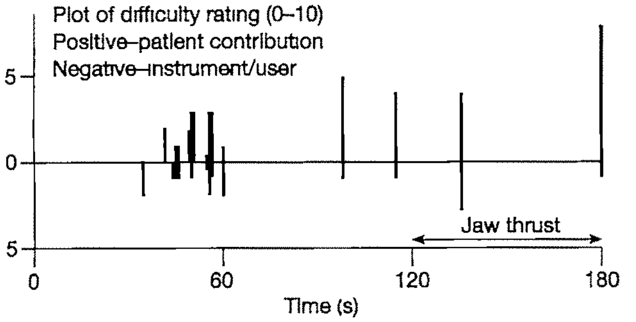


Fig 1 Graphical representation of instrumentation difficulty with individual patients.

representing difficulty in terms of time taken, rating score and relative patient *vs* instrument/user contribution (Fig. 1).

These results suggest that the Bonfils Intubating Fibrescope can be useful when used for routine orotracheal intubations. Jaw thrust appeared to be a helpful manoeuvre.

Acknowledgement: Karl Storz Endoscopy (UK) loaned the Bonfils Intubating Fibrescope.

Keywords: equipment, laryngoscopes fibreoptic

BIS—cautionary interpretation of data in children

M. S. Chawathe*, J. E. Hall*, J S Mecklenburgh and R. M Jones*

University of Wales College of Medicine, Cardiff, UK

Bispectral index or BIS is a processed EEG variable, derived from the EEG by a computer algorithm, scaled from 0–100, which is stated to reflect a patient's state of hypnosis and responsiveness.[1] Thus it claims to improve titration of anaesthetic agents and monitor risk of awareness. Experience to date suggests that BIS monitoring in children and infants should provide similar benefits to those in adults.[2] However, validation of BIS may present more of a challenge in children compared to adults, because the EEG in infants and children changes as the brain matures. The aim of our study was to analyse the interpretation of the BIS data collected in a study for gaseous induction in 60 ASA I and II children

In this preliminary work with BIS (using the Aspect 1000) we used data from a previous study of 60 ASA I–II children aged 5–10 yr undergoing gaseous induction with sevoflurane. BIS scores were measured preinduction, at loss of eyelash (LOE) reflex, at pupil size 2, and at 2 min and 4 min after LOE reflex. Regression analysis was used to determine any value of BIS in predicting heart rate and arterial pressure Mann–Whitney test was used to determine any difference in BIS between children experiencing apnoea or no apnoea. A $P<0.05$ was considered significant.

Excessive range of values of BIS, from 75 to 8 at pupil size 2, was detected in this study (Fig. 2). At 2 min after LOE reflex some individual values were as low as 5 and as high as 88, when the depth of anaesthesia should have approached stability in all children. The median BIS scores in the children with and without apnoea differed only by a non-significant 6%. There was no significant relationship between BIS values and heart rates and arterial pressures recorded at the corresponding time (R^2=0.01 and 0.09 respectively). Handedness of the individual and right- or left-sided placement of the BIS sensor were not noted during this study.

We conclude that the algorithm deemed suitable for adults appears not to be suitable for use in children in this retrospective study.

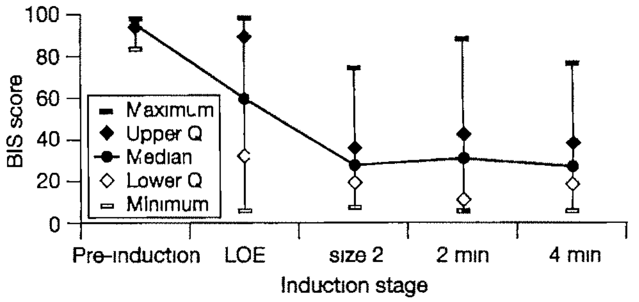


Fig 2 BIS scores during stages of induction.

Keywords: anaesthesia, depth; children

References

1 Sigl JC, Chamoun NC. *J Clin Monitoring* 1994; **10**: 392–404
2 Degoute CS, Macabeo C, Dubreuil R, *et al. Br J Anaesth* 2001, **86**. 209–12

A preliminary CoMFA model for chemically diverse intravenous general anaesthetics

J. C. Sewell and J W. Sear

Nuffield Department of Anaesthetics, University of Oxford, John Radcliffe Hospital, Headington, Oxford OX3 9DU, UK

We have previously demonstrated that molecular shape and electrostatic potential (a measure of charge distribution) are important determinants of activity in i.v. general anaesthetics.[1 2] The aim of this study was to derive an activity model based on the *spatial* distribution of these molecular properties, using comparative molecular field analysis (CoMFA).

A group of 14 chemically diverse i.v. general anaesthetics were considered. The free plasma concentrations (log EC_{50}) that abolish movement to a noxious stimulus were obtained from the literature. The anaesthetics were divided into a training set of nine compounds (eltanolone, minaxolone, Org 21465, pentobarbital, thiopental, methohexital, R-ketamine, propofol, chlormethiazole) used to formulate the activity model; and a test set of five agents (alphaxalone, thiamylal, Org 25435 (an alpha amino acid phenolic ester derivative), S-ketamine and R-etomidate) used to independently evaluate the model's predictability.

Computer-based structures of the anaesthetics were generated, and low energy conformers identified using a random search (SYBYL 6.7, Tripos Inc.). The conformers were aligned so as to maximize their similarity in shape and electrostatic potential to the most active agent in the group, eltanolone. The conformers with the highest similarity, calculated as Carbo indices (ASP 3.22, Accelrys Inc.), were retained. The aligned conformers were placed in a rectangular grid consisting of a lattice of points separated at 1Å intervals. The steric and electrostatic interaction energies between the anaesthetics and a probe atom (sp^3 carbon, +1 charge) at each grid point were evaluated, and correlated with *in vivo* potency (SYBYL). Thus an activity model was formulated, based on the spatial distribution of steric and electrostatic features of the anaesthetic molecules.

The final model explained 92.8% of the variance in the observed activities of the training set compounds (n=9, $P<0.001$). The model accurately predicted the potencies of three of the five test set agents. Org 25435 predicted log EC_{50}=5.44 (observed log EC_{50}=5.42), thiamylal 4.59 (4.81) and S-ketamine 5.28 (5.37). However, the model was less effective at predicting the activities of R-etomidate 5.08 (5.99) and alphaxalone 6 69 (5.06). Analysis of the relative contributions of the molecular properties at individual lattice points identified areas where the spatial distribution of molecular bulk and electrostatic potential are important in determining *in vivo* potency

The results demonstrate that a single CoMFA model with good predictability can be formulated for chemically diverse i.v. general anaesthetics The mapping of the spatial arrangement of the key electrostatic and steric features enabled the derivation of a preliminary three-dimensional 'pharmacophore' for i.v. anaesthetic activity.

Acknowledgement· This work was supported by a project grant from the *British Journal of Anaesthesia*

Keywords· anaesthetics, i.v.; model, computer simulation

References

1 Sewell JC, Sear JW, Halsey MJ. *Br J Anaesth* 1999, **82**. 470P
2 Sewell JC, Sear JW *Br J Anaesth* 2002, **88**. 166–74

Influence of fresh gas and circuit on induction of anaesthesia with sevoflurane

C. L. **Knaggs*** and G B Drummond

Department of Anaesthesia Critical Care and Pain Medicine, Royal Infirmary, 51 Little France Crescent, Edinburgh EH16 4SA, UK

Induction of anaesthesia with sevoflurane can be done with normal breathing using a low flow of oxygen as fresh gas.[1] Although this method maintains ventilation well, it must limit the rate of supply of anaesthetic to the patient. We studied the effects of different gas supply rates and circuits on inhalation induction

Sevoflurane was used to induce anaesthesia in otherwise healthy patients about to have gynaecological procedures. They were randomly allocated by sealed envelope to one of the following· oxygen 3 litre min^{-1} from a Bain circuit (group 3B), oxygen 6 litre min^{-1} from a Bain circuit (group 6B), or oxygen 9 litre min^{-1} from a Magill circuit (group 9M). We gave the sevoflurane by doubling the concentration from 0.5%, every three breaths, to 8%, and then maintaining that fresh gas concentration until loss of consciousness. The patient held her arm up at about 45° during induction We measured the time from first giving 8% to the time for the arm to come down to the horizontal, as the induction time. We measured the concentration of sevoflurane and carbon dioxide in the gas in the mask, and respired flow, and recorded these with an AD converter and computer. We calculated the best-fit polynomial to give an end-tidal sevoflurane concentration/time plot for the three groups. We compared the end-tidal concentrations at 30 s and the time to induction in the three groups by ANOVA and *post hoc* Bonferroni tests. Values are median (quartiles).

We asked 52 suitable patients to participate and 39 agreed. Of these, 37 were studied and 35 yielded adequate data. No patient had hypoxaemia or other adverse events. Table 3 shows the results.

There was no significant difference between induction times, although the sevoflurane concentration at 30 s was significantly less in the low flow group ($P<0.001$). End-tidal carbon dioxide was significantly less with the Magill circuit and 9 litre min^{-1}. We conclude that rebreathing may assist inhalation induction of anaesthesia

Table 3 Study parameters during induction with sevoflurane in three different groups

	Group 3B (n=14)	**Group 6B** (n=11)	**Group 9M** (n=10)
Time to induction (s)	64 (47–92)	48 (43–66)	57 (42–72)
End-tidal sevoflurane at 30 s %	2.0 (1.8–2.4)	3.0 (2.8–3.2)	3.0 (2.7–3.3)
End-tidal carbon dioxide (kPa)	5.5 (5.0–5.9)	4.8 (4.6–5.2)	4.2 (3.8–4.6)

Keywords: induction, anaesthesia; anaesthetic techniques, inhalation

Reference

1 Guracha Boru K, Drummond GB *Br J Anaesth* 1999; **83**: 650–3

Influence of oxygen therapy on heart rate after abdominal surgery

T. P. Banerjee*, A F Nimmo and G B. Drummond

Department of Anaesthesia Critical Care and Pain Medicine, Royal Infirmary, 51 Little France Crescent, Edinburgh EH16 4SA, UK

In patients after major abdominal surgery, oxygen treatment has been reported to reduce heart rate, but the change in heart rate did not appear to correlate with the change in oxygen saturation.[1]

We were able to assess this effect in the course of analysis of data from a study comparing oxygenation at night in patients randomly allocated to receive epidural or patient-controlled analgesia (PCA). Patients were given oxygen or air by nasal cannula for alternate hours, for 6 h for the first two nights after surgery We continuously recorded the ECG, and oxygen saturation with a finger probe pulse oximeter (Ohmeda 3400) using commercial software (Cardas) We used the 'rate' output from the oximeter, and excluded periods of artefact from both recordings, when the pulse records did not correspond with the ECG record and when the oximeter pulse wave was erratic We recorded the mean heart rate in the last 40 min of each hour of treatment. We related the change in heart rate and change in oxygen saturation for each change in inspired gas. Patients who did not achieve satisfactory oxygen saturation while breathing air were automatically given oxygen so full records were not available in all cases. One patient was converted from epidural to PCA for the second night.

We had records available for 18 patients. Table 4 summarizes the results.

Oxygenation was more satisfactory on the first night, and the effects of oxygen on oxygen saturation were more clear-cut. There was no significant change in heart rate, either in the groups receiving epidural or PCA for analgesia, or overall

We conclude that there is no evidence, in these patients, that oxygen administration affects heart rate

Acknowledgement: The original study was funded by the Scottish Hospitals Endowment Trust.

Keywords. oxygen, saturation, heart, heart rate

Reference

1 Rosenberg-Adamsen S, Lie C, Bernhard A, Kehlet H, Rosenberg J *Anesthesiology* 1999; **90** 380–4

Table 4 Mean (SD) changes in all the eligible subjects (7 epidural, 11 PCA), for the five changes from one inspired gas to the other

	Epidural		**PCA**	
	Night 1	**Night 2**	**Night1**	**Night 2**
Change in oxygen saturation (%)	4 (2.8)	2.3 (2.7)	2.5 (2)	2.3 (2.5)
Change in heart rate (beats min^{-1})	0 (1.5)	0 (1.2)	0 (1.3)	-1 (1.4)

Haemodynamic effects of the prone position for spinal surgery: TIVA versus inhalation anaesthesia

P. S. Sudheer*, B Ateleanu*, J E Hall*, S. W. Logan* and M Harmer

Department of Anaesthetics, University Hospital of Wales, Cardiff CF14 4XN, UK

Recently, total intravenous anaesthesia (TIVA) using propofol has become a widely used anaesthetic technique. Recent work has suggested inhalation anaesthesia is associated with improved cardiovascular stability compared with propofol anaesthesia.[1] In the prone position, cardiac output (CO) is decreased because of decreased preload.[2] There are no data in the literature describing the influence of intravenous anaesthesia on haemodynamic stability in the prone position.[2] Consequently, a study was designed to ascertain relative cardiovascular stabilities of these two techniques in prone patients.

Forty patients aged 18–75 yr having lumbar spinal surgery were recruited. Patients were randomized to receive either propofol TIVA or INH anaesthesia using isoflurane together with fentanyl, morphine and vecuronium. The lungs were ventilated with tidal volumes of 7–10 ml kg^{-1}, respiratory rate of 8–12 bpm, PEEP=0, to maintain a PE'_{CO_2} of 4.5–5 kPa. We measured the CO, our primary variable, using the NICO monitor. NICO calculates the CO using the technique of 'differential Fick partial rebreathing'. The NICO also calculates the stroke volume and systemic vascular resistance. We also measured the mean arterial pressure and heart rate.

A two-way ANOVA performed on haemodynamic variables showed CO to be significantly more stable with inhalation than TIVA anaesthesia during patient rotation (Table 5).

Table 5 Haemodynamic changes on changing body position in anaesthetized patients Values are given as mean (SD)

Changes (%)	**Supine to prone**		**Prone to supine**	
	Inhalation	**TIVA**	**Inhalation**	**TIVA**
Cardiac output	−12 (10)	−23 (9)	18 (15)	29 (21)
Mean arterial pressure	−4 (12)	8 (25)	11 (21)	−9 (11)
Heart rate	2 (10)	3 (8)	12 (22)	12 (17)
SVR	15 (38)	40 (55)	−4 (21)	−10 (22)

We conclude that inhalation anaesthesia using isoflurane is more cardiovascularly stable than propofol TIVA when patients are turned prone and when they are turned supine again. We cannot exclude changes in pulmonary haemodynamics on moving to the prone position as the cause of these findings.

Keywords: position, prone; heart, cardiac output

References

1 Kirkbridge DA, Parker JL, Buggy DJ. *Anesth Analg* 2001; **93** 1185–7

2 Yokohama M, Ueda W, Hirakawa M, *et al. Acta Anaesthesiol Scand* 1991; **35**. 741–4

Comparison of flow guided versus conventional volume replacement in major elective surgery

S. M. Lowson*

Department of Anesthesiology, University of Virginia Health System, Charlottesville, Virginia, USA

Twenty-four patients scheduled for either nephrectomy or radical cystectomy were consecutively enrolled into the study. Exclusion criteria were current history of angina, significant chronic lung disease, morbid obesity, significant psychiatric history, and the need for more extensive surgery. All patients had an arterial line and thoracic epidural placed prior to induction of anaesthesia, and received a standardized anaesthetic consisting of a sufentanil infusion supplemented by an inhalation agent and neuromuscular relaxation. In the intervention group, the NICO$_2$ cardiac output monitor (Novametrix) was used to guide perioperative volume replacement The goal was to maintain the cardiac index above 3 litre min^{-1} m^{-2} throughout the case with either volume replacement or a dobutamine infusion if volume failed. In the control group, arterial pressure, heart rate and, where possible, urine output were used to guide resuscitative efforts. In both groups, the haemoglobin was maintained between 9 and 11 g dl^{-1} with packed red cell transfusions. Between group statistical comparisons were performed using the unpaired Student's *t*-test.

The NICO$_2$ monitor performed reliably in all cases and no patient was excluded because of failure of the device to provide consistent recordings. There was no difference in mean age between the NICO$_2$ (65 yr) and the control (57 yr) groups. The two outcome variables in which we were interested were speed of recovery of gastrointestinal function, as measured by the time to tolerating a soft diet, and time to hospital discharge Overall, the difference in the times to diet toleration (84 *vs* 113 h) and hospital discharge (5.1 *vs* 6.6 days) in the NICO$_2$ (n=12) *vs* control (n=12) group were not significantly different. However, examining the radical cystectomy patients separately (n=12) showed the time to diet toleration (123 *vs* 176 h) and hospital discharge (6.8 *vs* 9.3 days) was significantly different (P<0.05) between the NICO$_2$ *vs* control group. In contrast, in the nephrectomy patients (n=12) there was no difference in either time to diet toleration (46 *vs* 50 h) or hospital discharge (3.5 *vs* 3.8 days) between the NICO$_2$ *vs* control group. The mean duration of surgery was 9.0 h for a radical cystectomy *vs* 4.4 h for a nephrectomy (P<0.01), and the mean difference in intraoperative volume replacement was 15 *vs* 7.3 litres (P<0 01).

In summary, use of flow guided therapy to guide intraoperative resuscitative efforts significantly reduced the time to recovery of gastrointestinal function and hospital stay in patients undergoing extensive procedures associated with major intraoperative fluid shifts but it did not alter the hospital course of patients undergoing briefer and less extensive surgical resections.

Acknowledgement: funding source: Novametrix Inc., Wallingford, CT, USA.

Keywords: fluids, replacement; surgery

Fluid replacement during Picolax® bowel preparation: the consequences for anaesthesia

S T A. Vaughan*, **A. MacKillop***, J M Fryer*, A S. Laurence and S Forshaw*

Department of Anaesthetics. Preston, UK

Picolax® contains magnesium citrate, which acts as an osmotic laxative and sodium picosulphate, which decreases water and electrolyte absorption while increasing colonic motility. When used for preoperative bowel preparation, it can result in dehydration with consequent difficulties during anaesthesia.[1] Administration of preoperative fluid has been shown to mitigate this.[2] We investigated whether this would improve the stability of anaesthesia.

Fifty patients ASA I to III, presenting for major surgery necessitating bowel preparation were studied. Patients were weighed prior to administration of bowel preparation and again on the morning of surgery. All patients were premedicated with temazepam 20 mg and metoclopamide 10 mg orally. Patients were randomized after recruitment to control, or an intravenous preoperative fluid load of 2 litres of normal saline given on the night before surgery. A radial artery catheter was sited prior to induction of anaesthesia using thiopental to loss of eyelash reflex and vecuronium 0.1 mg kg^{-1}, given by an anaesthetist blind to the patient group. Patients were monitored for change in arterial pressure after induction and prior to intubation. Vasopressors were given, on the clinical judgement of the blinded anaesthetist. Intraoperative blood loss, fluid requirements and urine output were noted.

As expected, weight loss due to bowel preparation was significantly less in the fluid group (Table 6). Mean arterial pressure drop during induction did not reach statistical significance but the fall of systolic arterial pressure was highly significant between groups, as was the number of patients needing vasopressors during induction. Despite the use of similar fluid volumes during surgery, intraoperative urine output was significantly greater in the fluid group. Thiopental dose, duration of surgery and blood loss were similar in both groups.

Table 6 Weight loss and intraoperative variables. Values are median (range). $^{\dagger}P<0.01$ (Mann–Whitney), $^{**}P<0.01$ (Chi squared)

	Control (n=25)		Fluid group (n=25)
Weight change (kg)	−1.5 (−3.2 to 2.5)	†	0 (−1.5 to 1)
Systolic arterial pressure (mm Hg)	−44 (−87 to −17)	†	−31 (−80 to 10)
Mean arterial pressure (mm Hg)	−22 (−54 to 3)	ns	−15 (−49 to 15)
Number given vasopressor	10	**	0
Volume intraoperative fluids (litre)	4 (1.5–7.3)	ns	3.5 (2.1–7.3)
Urine output (ml)	150 (0–600)	†	312 (90–870)

Our study confirms that Picolax® causes preoperative dehydration, which exaggerates the hypotensive effects of anaesthetic induction agents. This can be offset by the administration of preoperative crystalloid, which also improves perioperative urine production. Administration of preoperative intravenous fluids could be of benefit to patients receiving Picolax® bowel preparation.

Keywords. fluids, replacement

References

1 Barker P, Hanning C, Trotter T. *Ann R Coll Surg Engl* 1992; **74**: 318–19
2 Sanders G, Mercer S, Saeb-Parsey, *et al* *Br J Surg* 2001; **88** 1363–5

Correlation between theoretical toxic dose of a mixture of local anaesthetics and complication rate in patients undergoing brachial plexus block: a prospective analysis of 571 cases

R. V. Martin*, P Smith* and S. K. Pal

St Andrew's Centre for Plastic Surgery and Burns, Broomfield Hospital, Chelmsford, Essex CM1 7ET, UK

It is common practice at St Andrew's Centre to perform axillary brachial plexus blocks in patients undergoing hand surgery. We employ a transarterial approach with a two-point injection technique. In an adult we use a mixture of 30 ml of 1% lidocaine and 20 ml of 0.5% bupivacaine with epinephrine 1:200 000. The maximum safe dose of lidocaine with epinephrine is 7 mg kg^{-1} and that for bupivacaine[1] with or without epinephrine is 2 mg kg^{-1}. However, there are few references in the literature to the maximum safe dose of a mixture of local anaesthetics.[2]

We would like to introduce the concept of a Theoretical Toxic Dose Index (TTDI). It is the dose of lidocaine (mg kg^{-1}) divided by 7 plus the dose of bupivacaine (mg kg^{-1}) divided by 2. A safe index would be <1.

The data of 571 patients undergoing brachial plexus block were analysed. Any complications were recorded. The TTDI were calculated and correlated with rate of complications attributable to local anaesthetics. The results are shown in Table 7. Our overall success rate for the block was 87% for all grades of anaesthetists, rising to 95% with local anaesthetic supplementation. When the TTDI data were categorized (0–0.5, 0.5–1.0; 1.0–1.5; 1.5–2.0) it was found that the proportion of complication increased (linear regression, n=4, P=0.06) with a high predictability (r^2=0.88).

Table 7 Relationship of TTDI with success and complication rates

TTDI	Total	Success rate (%)	Success with LA	Complication	Complication rate (%)
<1	83	82	91	1	1.2
1.0–1.5	436	88	97	6	1.4
>1.5	52	90	96	1	1.9
Total	571	87	95	8	1.4

We conclude that in our series of patients our current practice is associated with a good success rate and low number of complications. The complications were minor and occurred at the time of injection. It would be prudent to obtain more data on the relationship between TTDI and complication.

Keywords: anaesthetics local, anaesthetic techniques, regional, brachial plexus

References

1 Pinnock C, Lin T, Smith T *Fundamentals of Anaesthesia* London Greenwich Medical Media Ltd., 1999
2 De Jong RH, Bonin JD. *Anesthesiology* 1981, **54**: 177–81

Evaluation of personal, environmental and biological exposure of paediatric anaesthetists to sevoflurane

N. Raj*, K A Henderson*, J E. Hall*, B Williams* and M Harmer

Department of Anaesthetics and Intensive Care Medicine, University of Wales College of Medicine, Cardiff CF14 4XN, UK

Paediatric anaesthetists have a higher degree of exposure than adult anaesthetists to waste anaesthetic gases especially during induction[1] and in non-theatre venues.[2] This study investigated the acute exposure of paediatric anaesthetists in theatre and other venues to sevoflurane and any association between the exposure and anaesthetic technique. Five lists each in four venues were targeted: MRI Suite, Day Surgery Unit, Oncology Unit and Dental

Theatre. Blood samples were collected at baseline and immediately following each induction throughout each list. All samples were measured using headspace analysis by gas chromatography and the concentration in blood calculated. A note was made of type of induction, airway management, circuit used and presence or absence of scavenging.

The exposure indices for blood sevoflurane were generally very low in all venues and did not exceed the Time Weighted Average limit of 20 ppm set by Abbot. Unpaired *t*-test with Bonferroni correction was applied to determine if there was any significant relationship between blood sevoflurane levels and the type of induction technique, airway control, breathing system or scavenging used (Table 8). Induction type and airway control made no difference to blood sevoflurane level, whereas predictably, breathing system type and presence of scavenging did have a significant effect ($P<0.001$).

Acknowledgement: funding provided by Association of Anaesthetists of Great Britain and Ireland.

Keywords: anaesthetics volatile, sevoflurane; anaesthetics volatile, atmospheric pollution

References

1 Henderson KA, Matthews IP. *Eur J Anaesthesiol* 2000; **17**· 149–51
2 Hoerauf KH, Wallner T, Akca O, *et al* *Anesth Analg* 1999; **88**· 925–9

Thigh rotation and the anterior approach to the sciatic nerve; an MRI study

C. S. Moore, J. A W Wildsmith and D E. Sheppard*

University Department of Anaesthesia, Ninewells Hospital, Dundee, UK

The anterior approach to the sciatic nerve block may be associated with a high failure rate because the nerve lies posterior to the lesser trochanter of the femur at the level of needle insertion.[1] However, previous work using cadavers[2 3] demonstrated that internal rotation of the leg renders the nerve more accessible to the anterior approach. We wished to examine this relationship *in vivo*

After ethics committee approval, five male and five female volunteers consented to undergo magnetic resonance imaging. A vitamin E marker was placed on the surface where a needle would have been inserted for an anterior approach to the sciatic nerve.[4] Three scans were then performed, one with both legs in the neutral position, the next with maximal bilateral internal rotation at the hip and the third with maximal bilateral external rotation at the hip. The scans were then examined with a consultant radiologist. The line of sight from the insertion point to the sciatic nerve was examined, and the distance from the skin to the nerve measured, as were the distances from the line of sight to both the femoral artery and nerve

Table 9 Results are given as numbers (out of 10) or mean distances (mm) LOS=line of sight

	Position					
	External rotation		Neutral position		Internal rotation	
	Left	Right	Left	Right	Left	Right
Direct LOS to sciatic n	1	0	6	6	9	8
Direct LOS through fem art	3	0	3	1	1	0
Direct LOS through fem n.	4	4	1	0	1	1
Distance from skin to sciatic n	106	108	107	106	109	109
Distance from LOS to fem art	7	10	10	11	13	14
Distance from LOS to fem n.	5	5	5	4	8	8

The mean age was 30 (range 21–44) yr and the mean body mass index was 24 (19.5–28). Other results are shown in Table 9.

These results confirm that, as the thigh is moved from an externally to an internally rotated position, the sciatic nerve becomes more accessible by the anterior approach, and the risk of femoral artery or nerve puncture is reduced, but not eliminated.

Acknowledgement: CSM was supported by AstraZeneca Pharmaceuticals.

Keywords. anaesthetic techniques, regional, sciatic

References

1 Charlton JE, Nicholls BJ, White E *Br J Anaesth* 1987; **59**: 127P
2 Hadzic A, Reiss W, Dilberovic F, *et al. Reg Anesth Pain Med* 2001; **23** (May–June supplement): 38
3 Vloka JD, Hadzic A, April E, *et al. Anesth Analg* 2001; **92**: 460–2
4 Wildsmith JAW, Armitage EN (eds) *Principles & Practice of Regional Anaesthesia*, 2nd edn, 1993; 195–7

TNFα cleaving enzyme (TACE) activity assessed by TIMP-3 binding

H. J. Robertshaw* and F M Brennan*

Kennedy Institute of Rheumatology Division, Imperial College School of Medicine, 1 Aspenlea Road, London W6 8LH, UK

Circulating soluble tumour necrosis factor α (TNFα) is formed by the cleavage of membrane-bound TNFα by a membrane-bound metalloproteinase (TNFα cleaving enzyme, TACE).[1] The natural inhibitor of TACE, tissue inhibitor of metalloproteinase-3 (TIMP-

Table 8 Blood sevoflurane levels expressed by induction technique for all staff at every induction, for each venue and percentage of technique used at each site Mean (SD) ppm for total cases and mean [range] ppm per list. IV=intravenous, IH=inhalational induction; LMA[†]=Laryngeal Mask Airway, ETT=tracheal tube, Other breathing system=circle or scavenged Bain *$P<0.001$. ([†]LMA is the property of Intavent Limited)

	Blood sevoflurane (all staff) (ppm)	Percentage technique used			
		MRI suite (*n*=5)	Day surgery (*n*=5)	Oncology (*n*=5)	Dental (*n*=5)
Induction (IV.IH)	3 (3) 3 (3)	37%· 63%	47% 53%	45%: 55%	94%· 6%
Airway control (Mask:LMA/ETT)	3 (3) 3 (3)	0% 100%	42% 58%	100%:0%	0%. 100%
System used (T piece other)	5 (3) 1 5 (3)*	100% 0%	64%. 36%	11%. 89%	0%· 100%
Scavenging (present:absent)	1.5 (3): 4.5 (3)*	0%. 100%	36%· 64%	89% 11%	100%: 0%
Blood sevoflurane each venue		4 6 [1–10]	4 2 [0–10]	2 8 [0–13]	1 4 [0–13]

3), has been shown to bind selectively to active TACE on the cell surface and the inhibitory activity of TIMP-3 lies within the N-terminus.[2] We used these properties of TIMP-3 to develop an assay for TACE catalytic activity using flow cytometry and so examine TACE activity following cell stimulation.

Elutriated human monocytes (1×10^6 cells well^{-1}) were stimulated with lipopolysaccharide (LPS 10 ng ml^{-1}) and harvested at time points shown. At harvest, in one group TACE surface protein expression was measured by flow cytometry (using optimized antibody combination). To the other group, histidine-labelled N-TIMP-3 was added and detected by flow cytometry using anti-histidine antibodies. Flow cytometry data are expressed as mean fluorescence intensity (MFI) ±SD from seven experiments (10 000 cells in each experiment).

Upon LPS stimulation, TACE was rapidly lost from the cell surface (Fig. 3A), confirming previous work which examined TACE using confocal microscopy.[3] This protein down-regulation at the cell surface coincides with maximal catalytic activity (Fig. 3B). These findings support the hypothesis that inactive TACE is expressed on the cell surface and then rapidly removed from the cell surface following cell activation.

Acknowledgement: This work was funded by a grant from the Arthritis Research Council, UK.

Keywords: enzymes, tumour necrosis factor α cleaving enzyme

References

1 Black RA, Rauch CT, Kozlosky CJ, *et al* *Nature* 1997: **385**; 729–3
2 Amour A, Slocombe PM, Webster A, *et al*. *FEBS Lett* 1998: **435**; 39–44
3 Doedens JR, Black RA. *J Biol Chem* 2000: **275**: 14598–607

Respiratory monitoring of non-intubated patients using the 'PIPPA' breathing monitor

D. Sankar* and K J Kim*
Rochdale Health Care NHS Trust, Rochdale Infirmary, Rochdale, UK

Increasingly, with the development of newer protocols in clinical practice, there is a need for monitoring respiration. The most commonly used technique for this purpose is human observation. Capnography and changes in transthoracic impedance are potential alternatives but have not found widespread acceptance. With capnography a nasal cannula is required, the equipment is expensive and cumbersome and regular calibration is needed. In contrast, transthoracic impedance changes are extremely sensitive to patient movement, demonstrate slow response times and do not recognize apnoea rapidly enough. Human observation of large numbers of patients is a near impossible task.

In 1999 a new simple respiratory rate monitor based on the pyroelectric polymer sensor (PEP) was described and evaluated.[1] It was concluded that, in the laboratory, the PEP sensor performed well and appeared to have many desirable features If these advantages were maintained in a clinical setting such a system would compare favourably with existing methods and may be valuable in cases of acute illness, major injury and perioperative care.

We received on loan a prototype of the PIPPA Breathing Monitor. After approval of the local ethics committee and the medical devices agency, we chose to study four groups of patients as follows: a control group, patients receiving supplemental oxygen therapy, patients receiving nebulized medication and patients receiving humidified oxygen treatment. The measurements made by the PIPPA were compared with those obtained simultaneously by the use of transthoracic impedance from the ECG monitor and human observation by nurses as part of their regular monitoring. The target number of patients in each group is 50. The results are only being presented for the control group and the nebulized medication group as the others are not yet complete Results are summarized in Table 10. The PIPPA monitor correlates well with both human observation and transthoracic impedance.

Keywords: monitoring, ventilation

Reference

1 Dodds D, Purdy J, Moulton C The PEP transducer A new way of measuring respiratory rate in the non-intubated patient *J Acc Emerg Med* 1999; **16**· 26–8

Table 10 Coefficient of correlation between PIPPA and the ECG monitor (r1), between PIPPA and the nurse observer (r2) and between ECG monitor and nurse observer (r3)

Group	Number of patients	Number of observations	r1	r2	r3
Control	50	100	0.73	0.91	0.75
Nebulized medication	50	241	0.84	0.90	0.85

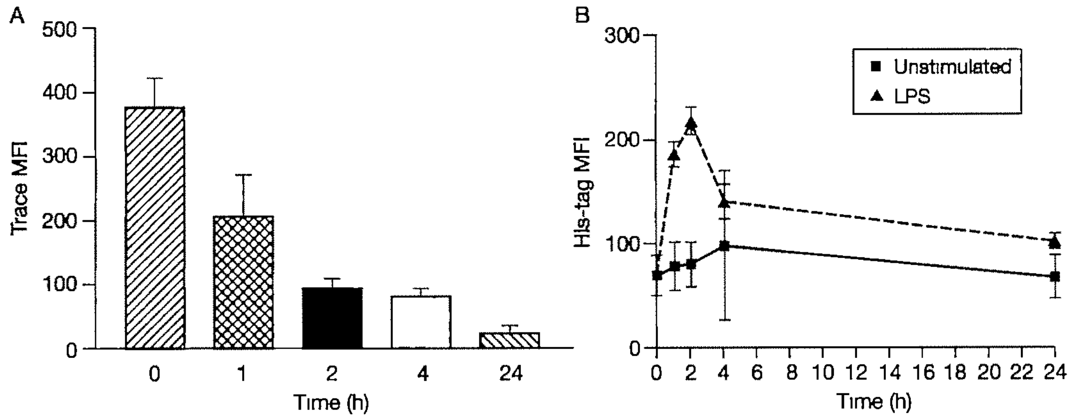


Fig 3 Time course of TACE protein (A) and TACE activity (B) in LPS-stimulated monocytes.

Actigraphic measurements of sleep variables and circadian rhythm in chronic pain patients compared with healthy controls

M. Schupp*, N. A. Hall*, P. Sharpe and D. J. Rowbotham

University of Leicester and University Hospitals of Leicester NHS Trust, Leicester, UK

Sleep disturbance is a significant problem for chronic pain patients. Furthermore insomnia may indicate severity of chronic pain symptoms and psychological disturbance.[1] Actigraphy is the study of sleep via movement using a wristwatch containing a small accelerometer and data logger which is worn on the patient's non-dominant arm. Frequency and amplitude of movement are logged at 1-min intervals throughout the observation period. Data are processed using Actiwatch Sleepwatch software (Cambridge Neurotechnology®). It may be worn for several weeks at a time. It monitors sleep in the home environment, reducing the impact of 'first-night' effects seen in laboratory assessments of sleep.[2]

We used a combination of sleep diaries and activity monitoring (actigraphy) to assess the presence and magnitude of sleep disturbance in the patient groups. We studied 21 adult subjects, eight volunteers without any symptoms of chronic pain and 13 patients from the pain clinic. Following written informed consent they were asked to wear the monitor for a 2-week period and complete a daily sleep diary.

The watch was well tolerated in all groups. There were no differences in actual sleep time, sleep efficiency or sleep bouts. Fragmentation index score was significantly higher in the chronic pain group ($P<0.001$). Measures of circadian rhythm such as intradaily stability, intradaily variability and relative amplitude were measured with conventional sleep variables and were similar between groups. Data were analysed using SPSS v11.0. Sleep variables were analysed with Student's *t*-test and circadian rhythm with Mann–Whitney U test.

The fragmentation index is the addition of the percentage time spent moving and the percentage of immobility phases of 1 min, this is used as an indicator of restlessness The fragmentation index scores were significantly higher in the pain group whilst other sleep variables remained the same (Table 11). It is possible that this index may relate to quality of sleep; however, more work is required to validate this thoroughly.

Keywords. pain, chronic; sleep

References

1 Wittig RM, Zorick FJ, Blumer D, *et al. J Nerv Ment Dis* 1982, **170**. 429–31

2 Jean LG, von Gizycki H, Zizi F, *et al. Precept Mot Skills* 1997; **85**: 219–16

Table 11 Actual sleep time (min), actual sleep (%), sleep bouts and fragmentation index (mean (SD))

	Control	Pain	*P* (Student's)
AST (min)	387 8 (60 36)	386 0 (100 25)	0 96
AS (%)	90 69 (4 84)	81.10 (18.05)	0 16
SB	19 55 (8.44)	29 72 (20 26)	0 19
FI	25 89 (8 87)	59.21 (21 26)	0 001

Change in snoring as a predictive factor for pre-eclampsia

M. Dolling*, P. Sharpe and C. D. Hanning

University Department of Anaesthesia, Critical Care and Pain Management, University Hospitals of Leicester, Leicester Royal Infirmary, Leicester LE1 5WW, UK

The amount and quality of sleep changes with pregnancy.[1] There is growing evidence of a link between snoring, sleep disordered breathing and pre-eclampsia.[2] Pre-eclampsia is a major cause of maternal and neonatal morbidity and mortality.[3]

Patients were approached within 24 h of delivery and asked to complete a simple questionnaire, with the aid of a research midwife. The questionnaire was used to record demographic data (including date of birth, ethnicity, smoking history, alcohol and illicit drug consumption), previous medical and relevant family history, obstetric history, and sleep history (focusing on snoring, change in snoring, witnessed apnoeas, Epworth sleepiness score) and clinical data from case records.

Data were collected from 609 patients of whom 53 had proteinuric hypertension and were treated by the obstetricians as suffering from pre-eclampsia.

Several sleep-related variables were significantly different in the pre-eclamptic group (Table 12). Logistic regression analysis was employed and demonstrated a highly significant correlation between worsening snoring during pregnancy and pre-eclampsia. A prospective study is required to demonstrate the presence of upper airways resistance syndrome in this group of patients and subsequently measure any beneficial effects of continuous positive airway pressure therapy.

Table 12 Incidence of snoring in different groups

	Normal	Hypertension	Proteinuric hypertension	*P* value
New snoring in pregnancy				
No	188	5	11	<0 001
Sometimes	208	4	17	
Often	97	2	12	
Nightly	44	5	13	
Snoring worse during pregnancy				
Yes	116	5	25	0 01
No	168	4	13	
Epworth sleepiness score				
9 or less	344	9	24	0 02
10 or more	176	7	27	

Keywords: complications, pre-eclampsia; sleep

References

1 Feinsilver SH, Hertz G. *Clin Chest Med* 1992; **13**: 637–44

2 Edwards N. *Am Family Physician* 1993; **60**· 1792

3 Department of Health. *Why Mothers Die*. Report on confidential enquiries into maternal deaths in the United Kingdom, 1994–6

Effect of remifentanil on postoperative pain in patients having fentanyl–propofol anaesthesia for cardiac surgery

K. Rauf*, A. Vohra, P Fernandez-Jimenez*, M Forrest* and N O'Keeffe*

Department of Anaesthesia, Manchester Royal Infirmary, Manchester, UK

Remifentanil is an ultra-short acting opioid. During anaesthesia it provides intense analgesia and sympatholysis that is ideal for cardiac surgery. Postoperative agitation and increased analgesic requirement after remifentanil infusion may be a problem. Studies in non-cardiac surgery have shown mixed results.[1 2] This prospective double-blind randomized study assesses the effect of remifentanil on postoperative recovery expressed as increased analgesic requirement after off-pump coronary artery bypass surgery (OPCAB).

Twenty patients undergoing elective OPCAB were randomly assigned to receive infusions of remifentanil ($50\,\mu g\,ml^{-1}$ at $0.12\,ml\,kg^{-1}\,h^{-1}=0.1\,\mu g\,kg^{-1}\,min^{-1}$) (group R, n=10); or saline (at $0.12\,ml\,kg^{-1}\,h^{-1}$) (group S, n=10). Anaesthesia was standardized with target controlled propofol infusion (1.8–$4\,\mu g\,ml^{-1}$) and fentanyl ($15\,\mu g\,kg^{-1}$). After surgery, propofol (1.5–3 $mg\,kg^{-1}\,h^{-1}$) and the study solution were continued until the patient was ready to be woken up (warm and cardiovascularly stable). Morphine infusion (0.015–0.02 $mg\,kg^{-1}$) was also started immediately after operation with additional boluses (1–2 mg) as assessed by pain scores (VAS 0–10). Morphine requirements were noted as total morphine before stopping sedation (Mpre), morphine in the first hour after stopping sedation (M1) and total morphine in 12 postoperative hours (M12). Patient data including height, weight, duration of surgery (op time) and of sedation (sedn time) were recorded. Student's t-test and Mann–Whitney U test were used for data analysis (*$P<0.05$ significance level).

In the first hour after discontinuing sedation, morphine requirement was higher in group R as compared to group S, but similar in the period till sedation was stopped and in 12 h after surgery. There was no difference in pain scores (median (range) R=5 (2–9), S=3 (0–7)). Table 13 shows mean (SD).

We conclude that remifentanil infusion is associated with an increased requirement of morphine in the first hour after discontinuation, in spite of preloading by fentanyl.

Keywords: analgesics opioid, remifentanil; surgery, cardiovascular

References

1 Guignard B, Bossard A, Coste C, *et al. Anesthesiology* 2000; **93**. 409–17
2 Cortinez I, Brandes V, *et al. Br J Anaesth* 2001, **87**: 866–9

Table 13 Morphine requirement in the two groups

	Op time (min)	Sed time (min)	Mpre (mg)	M1 (mg)	M12 (mg)
Group R	196 (53)	264 (97)	9.3 (2.6)	8.15 (3.6)*	27.1 (8.3)
Group S	198 (35)	226 (91)	8.7 (3.3)	3.29 (2.3)*	24.0 (6.3)

Urgency of Caesarean section, time to delivery and fetal outcome: a prospective observational study

N. Patel*, R Fernando and V Sodhi

Department of Anaesthesia, Royal Free Hospital, London NW3 2QG, UK

Although the urgency of Caesarean section (CS) has recently been classified,[1] its relationship with fetal outcome is unclear. Our aim was to identify any association between the grade of urgency and markers of fetal condition at birth such as Apgar scores and umbilical cord arterial (UA) and venous (Uv) blood gases. The influence of the time interval taken to establish regional anaesthesia (RA) as well as surgical delivery times were also assessed.

This prospective observational study was conducted in our unit over a 4-month period, collecting data from 203 consecutive CSs performed under regional anaesthesia. Data included: grade of CS (1, Emergency; 2, Urgent; 3, Scheduled; 4, Elective), type of RA technique (spinal or epidural top up of a pre-existing labour epidural), RA injection to T4 sensory block time, injection to knife-to-skin (KTS) time, KTS to delivery time, uterine incision (UI) to delivery time, Apgar scores at 1 and 5 min, umbilical cord pH, $[H^+]$ and base excess. Statistical analysis included a modified Levene equal variance test, analysis of covariance (ANCOVA) and linear trend analysis using a general linear model ($P<0.05$). RA technique was analysed on an intention to treat basis.

Age, height, weight, gestation and parity did not differ between groups. There were two conversions to general anaesthesia after failed RA: one pre-delivery and one post-delivery.

Apgar score at 1 min improved significantly, as did Uv pH and $[H^+]$ with reducing urgency of CS (1 to 4) (Table 14). A corresponding trend for UA pH and $[H^+]$ was not identified. The significantly longer times to T4 block and KTS with reducing CS urgency were not confounding variables in terms of fetal outcome measures. Further verification with larger patient numbers is required.

Acknowledgement: Obstetric Anaesthetists' Association funded research fellowship (NP).

Keywords: anaesthesia, obstetric

Reference

1 Lucas DN, Yentis SM, Kinsella SM, *et al. J R Soc Med* 2000, **93** 346–50

Table 14 Data are number (n), mean (SD) or median [IQR], *$P<0.001$, **$P<0.0001$ (linear trend)

	Grade 1 (n=18)	Grade 2 (n=83)	Grade 3 (n=19)	Grade 4 (n=83)
Spinal/Epidural Topup (n)	9/9	28/55	14/5	80/3
Injection to T4 block (min)	7.50 (2.31)	12.68 (6.95)	10.89 (5.92)	12.16 (6.56)*
Injection to KTS (min)	12.17 (6.40)	21.55 (10.39)	22.21 (9.10)	26.30 (10.27)**
KTS to delivery (min)	7.50 (4.73)	9.14 (6.37)	11.21 (6.48)	10.13 (7.68)
UI to delivery (min)	3.12 (3.66)	2.23 (1.86)	2.50 (1.47)	2.01 (1.20)
Apgar 1 min	8.5 [5.25–9]	9 [8–9]	9 [8–9]	9 [9–9]**
Apgar 5 min	10 [9.25–10]	10 [10–10]	10 [9.75–10]	10 [10–10]
UA pH	7.22 (0.09)	7.25 (0.06)	7.27 (0.05)	7.27 (0.06)
UA $[H^+]$ (nmol $litre^{-1}$)	62.10 (13.76)	56.49 (8.66)	54.51 (6.72)	54.47 (9.03)
UA Base Excess (mmol $litre^{-1}$)	–8.00 (4.53)	–6.98 (3.81)	–4.17 (2.33)	–5.73 (3.05)
Uv pH	7.26 (0.09)	7.30 (0.06)	7.31 (0.04)	7.32 (0.04)**
Uv $[H^+]$ (nmol $litre^{-1}$)	56.40 (13.35)	50.31 (6.71)	48.21 (4.48)	48.14 (4.92)**
Uv base excess (mmol $litre^{-1}$)	–7.49 (3.47)	–7.38 (2.99)	–5.99 (2.29)	–5.56 (2.17)

POSTER PRESENTATIONS

The effectiveness of the Neuropen in predicting the dermatomal limits of sensory blockade in regional anaesthesia for Caesarean section as compared with ethyl chloride

M. Dolling*, N. Roberts* and P. Sharpe

University Department of Anaesthesia, Critical Care and Pain Management, University Hospitals of Leicester, Leicester Royal Infirmary, Leicester LE1 5WW, UK

Ethyl chloride is commonly used to define the limits of sensory block for regional anaesthesia. This volatile agent is a chlorocarbon that is both explosive and an atmospheric pollutant.[1] Other methods have been tested for assessing sensory blockade but all possess their own limitations. It has been demonstrated that when using a needle the recorded dermatomal level can be about two dermatomes below that of ethyl chloride.[2]

In this study we have tested a device (the Neuropen) that is employed in medical practice as a means of assessing sensory neuropathy. It works by applying a constant (40 g) pressure via a blunt sprung disposable stylet, applied to the skin in a dabbing motion in the same way a needle might be used.

Forty patients were recruited who were booked for elective Caesarean section. There was one participant who withdrew. Each patient received a standardized combined spinal–epidural anaesthetic. Two investigators then independently recorded the level of the block in a caudal to cephalic direction and then cephalic to caudal, one using the Neuropen and one ethyl chloride spray. These recordings were made at 15 min and 1.5 h after insertion of the spinal component.

The data were analysed using a Bland Altman plot. Mean and standard deviations were calculated for the differences between methods. These figures were then used to calculate the limits of agreement between ethyl chloride and Neuropen (Fig. 4).

The Neuropen provides a means of defining height of a sensory block within three dermatomes of ethyl chloride.

Keywords: sensory block, anaesthetic techniques, regional

References

1 Aitkenhead AR, Smith G. *Textbook of Anaesthesia*, 3rd Edn Edinburgh: Churchill Livingstone, 1996; 297
2 Greene NM. *Anesthesiology* 1958; **19**. 45–50

Recording postoperative pain in ambulatory surgery: further evaluation of a revised electronic data collection device

P. Watt*, J. Williams*, A. Roscoe*, E. Pallett*, P. Maslowski*, J. P. Thompson* and D Rowbotham

University Department of Anaesthesia, Critical Care & Pain Management, Leicester Royal Infirmary, Leicester LE1 5WW, UK

The Visual Analogue Scale (VAS) is widely used in the assessment of postoperative pain. However, it may generate data storage problems and errors when data are transferred to a computer for analysis. We have refined a previous automatic data collection device to incorporate a slider and digital display (the EPIC slide). This device records VAS scores on a 0–100 mm scale and the data are automatically tagged with time and date. In addition, it can ask and store responses to other questions.

Forty patients aged 18–65 yr undergoing ambulatory surgery were enrolled. The investigators made three postoperative visits at 0.5, 1 and 2 h. At each visit patients were asked to perform four VAS pain scores, two using the new EPIC slide device and two using a card VAS slider. Between readings a distraction question was asked regarding the patients preferred method of measurement, plus a verbal assessment of pain. The patient was blinded to

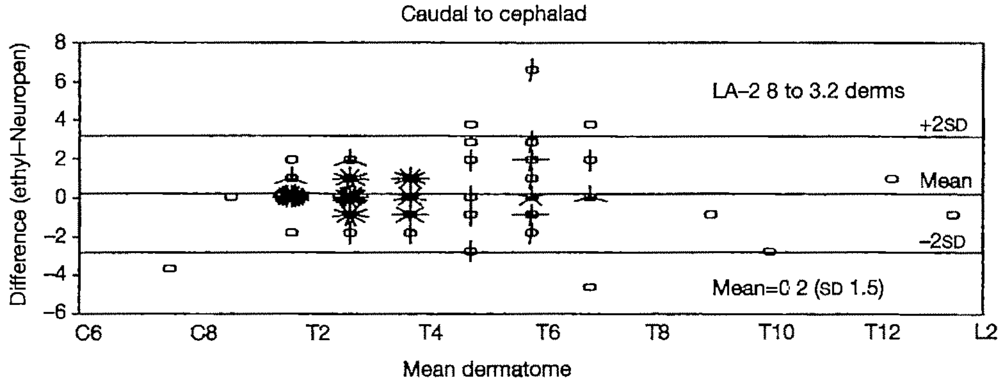


Fig 4 Limits of agreement (LA) using Bland Altman plot for the difference between ethyl chloride and Neuropen.

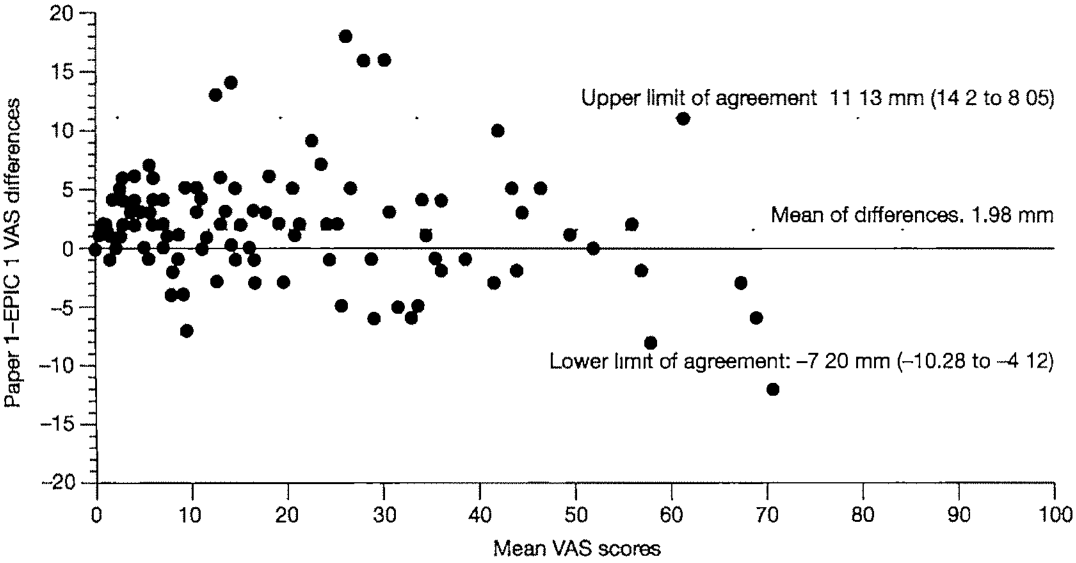


Fig 5 Limits of agreement using Bland Altman plot of mean VAS scores detremined using a VAS card or an EPIC slide device

exact measurements of all readings. Data were analyzed using a Bland Altman plot (Fig 5). Mean and standard deviations were calculated for the differences in VAS pain scores of the two measurement methods and for repeatability within each method. Analysis showed good agreement between the methods with a mean difference of 1 98 mm, limits of agreement 11.13 to -7.2 mm (95% CI -10.8 to 14.2 mm) (Fig. 5).

The EPIC slide system was generally well received by patients, with two thirds expressing a preference for this method of data collection. The remaining one third of patients expressed no preference and no one expressed a preference for the card VAS.

Keywords. pain, postoperative; surgery, day-case

References

1 DeLoach LJ, Higgins MS, Caplan AB, *et al. Anesth Analg* 1998, **86**: 102-6
2 Anderson I, Dolling M, Pallet E, *et al Br J Anaesth* 2002; **88**· 328P

Guide to Contributors

The purpose of the *British Journal of Anaesthesia* is the publication of original work in all branches of anaesthesia, including the application of basic sciences. One issue each year deals mainly with material of postgraduate educational value.

Papers for publication and all editorial communications should be addressed to: Professor J. M. Hunter, Editor-in-Chief, *British Journal of Anaesthesia*, University Department of Anaesthesia, Royal Liverpool University Hospital, The Duncan Building, Daulby Street, Liverpool L69 3GA, UK. Tel./Fax: +44 (0) 151 706 4005. E-mail: bja@liv.ac.uk

Papers

Papers submitted must not have been published in whole or in part in any other journal, and are subject to editorial revision. It is a condition of acceptance for publication that copyright becomes vested in the journal and permission to republish must be obtained from the publisher.

Papers based on clinical investigation should conform to ethical standards as set out in the Declaration of Helsinki and should normally include a statement of approval from an appropriate Ethics Committee. In the case of animal studies it is the responsibility of the author to satisfy the Board that no unnecessary suffering has been inflicted. Studies from the UK should specify the Home Office Licence number; from elsewhere, a statement of approval from an appropriate licensing authority.

Legal considerations

Authors should avoid the use of names, initials and hospital numbers which might lead to recognition of a patient. A patient must not be recognizable in photographs unless written consent of the subject has been obtained. A table or illustration that has been published elsewhere should be accompanied by a statement that permission for reproduction has been obtained from the authors and publishers.

Preparation of manuscript

Four copies of each manuscript (including revised texts) should be submitted and should indicate the title of the paper, the name(s), full address(es) of the author(s), and be in letter quality heavy type (not dot matrix), double-spaced on one side only of the paper, with a wide margin. Contributors should retain a copy in order to check proofs and in case of loss. Where possible, manuscripts should also be submitted on disk. Our preferred format is a 3.5″ PC floppy disk with the file written in Word 6 for Windows. However, it is also possible to process disks submitted in other formats, provided sufficient information is supplied to enable conversion to the preferred format. Articles on disk should be prepared in the simplest possible form. Please do not use endnotes, footnotes, etc. for references. Correct fonts, type sizes, column measures, etc, will be added by the technical editor.

Each of the four copies submitted must be accompanied by a complete set of figures. One set of figures must be unmounted glossy prints (see below); the three other sets may be photocopies.

Manuscripts should be accompanied by a formal letter of request for publication which should be signed by all the authors. There should be a clear declaration of any financial or commercial interest which any author may have in the material. The Editor may wish to see raw data if necessary.

Papers in recent issues of *British Journal of Anaesthesia* should be consulted for general and detailed presentation. They are most often subdivided into:

- Title page
- Summary, including Keywords
- Introduction (not headed)
- Methods
- Results
- Discussion
- Acknowledgements
- List of references
- Tables (including legends to tables)
- Illustrations (including captions)

Title page

There should be a separate title page, including the name(s) and address(es) of all author(s). It should be made clear which address relates to which author. Authors' present addresses differing from those at which the work was carried out, or special instructions concerning the address for correspondence, should be given and referenced at the appropriate place in the author list by superscript numbers. If the address to which proofs should be sent is not that of the first-mentioned author, clear instructions should be given in a covering note and not on the title page. The title page should be paginated as page 1 of the paper.

A short running title containing not more than 50 characters and spacing should be included.

Summary

The summary will be printed at the beginning of the paper. It should be on a separate sheet, in structured format (Background; Methods; Results; and Conclusions) for all original articles (Clinical Investigations, Laboratory

©The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Investigations, and Short Communications) but not for Reviews, Case Reports, or Commentaries. It should give a succinct account of the problem, in up to 250 words. It may be used as it stands by abstracting journals. References are not used in this section, except in exceptional circumstances.

Three to five key words or phrases (for indexing) should be included below the summary.

Introduction

The introduction should give a concise account of the background of the problem and the object of the investigation. Previous work should be quoted only if it has a direct bearing on the present problem.

Methods

Methods must be described in sufficient detail to allow the investigation to be interpreted and repeated by the reader. Any modification of previously published methods should be described and the reference given. If the methods are commonly used, only a reference to the original source is required.

Drugs

When a drug is first mentioned it should be given the international non-proprietary name, followed in parentheses by the chemical formula only if the structure is not well known, and by the capitalized proprietary name.

Results

Description of results, while concise, should permit repetition of the investigation by others. Data should not be repeated unnecessarily in text, tables and figures, and unwarranted numbers of digits should be avoided. Significance should be given as values of probability.

Discussion

The discussion should not merely recapitulate the results, but should present their interpretation against the background of existing knowledge. It should include a statement of any assumptions on which conclusions are based.

Acknowledgements

Acknowledgements will be printed in small type. They should be brief, and should include reference to sources of support and sources of drugs not freely available commercially. Individuals named must be given the opportunity to read the paper and approve their inclusion in the acknowledgements, before the paper is submitted.

References

There should be a list of references at the conclusion of the paper, commencing on a new sheet.

References must be numbered consecutively in the order in which they are first mentioned in the text, with the exception of review articles, when references should be arranged alphabetically.

References in text, tables and legend should be identified by arabic numbers appearing in the text in superscript, for example [5] or [5–7] or [5 16] for unrelated references. When a table or figure is first mentioned, its reference must continue the sequence.

Use the style of references adopted by the US National Library of Medicine and used in *Index Medicus*. The titles of journals should be abbreviated.

The names and initials of more than six authors should be abbreviated to three authors followed by *et al.*

Text references to 'unpublished observations' or 'personal communications' should not be included in the final list of references. Authors are responsible for verifying that the wording of references to unpublished work is approved by the persons concerned. Papers which have been submitted and accepted for publication should be included in the list, the phrase 'in press' replacing volume and page number. Information from manuscripts submitted but not yet accepted should be cited in the text as unpublished observations.

Examples of correct forms of references:

Journals:

1. Brown BR jr, Gandolphi AJ. Adverse effects of volatile anaesthetics. *Br J Anaesth* 1987, **59** 14-23

Chapter in a book:

2 Hull CJ Opioid infusions for the management of postoperative pain. In: Smith G, Covino BG, eds. *Acute Pain* London Butterworths, 1985; 155-79

Monographs:

3 Moore, DC. *Regional Block*, 4th Edn. Springfield, Illinois Charles C Thomas, 1979

Restrict references to those that have direct bearing on the work described and cite only references to books and articles published in *Index Medicus* journals.

It is essential that authors verify the content and detail of references which they list against the original articles, as this responsibility cannot be accepted by either Editors or publishers.

Tables

All tables should be on separate sheets and be capable, with their captions, of interpretation without reference to the text. They should be numbered consecutively with Arabic numerals. Units in which results are expressed should be given in brackets at the top of each column, and not repeated on each line of the table. Ditto signs are not used. Footnotes are not used.

Illustrations

Photographs should be unmounted glossy prints, and should be protected adequately for mailing. Surfaces should not

be marred with clips, pins or by heavy writing on the back. Drawings, charts and graphs should be in black indict ink on white paper and, if in sets, should be presented at a uniform magnification. Illustrations should be clearly numbered on the back, preferably in soft pencil, with reference to the text, and using Arabic numbers. They should be accompanied on a separate sheet by a suitable legend. Lettering should be professional-looking, uniform, preferably in a common typeface, large enough to read at a reduced size, and in proportion to the illustrated material. Lines in the original must also be thick enough to allow for reduction. Magnifications, especially in photomicrographs, should be indicated by a scale on the photograph itself, in order to remain appropriate after reduction. Symbols which are to appear in the figure (and not in the legend) should be chosen from the following available types:

● ○ ■ □ ▼ ▽ ▲ △ ◆ ◇ × +

The names of the author and title of the paper should also be written in soft pencil on the back of the illustrations.

It should be noted that A4-size figures generated by computer are usually unacceptable (see Extended Guide to Contributors—*Br J Anaesth* 2000; **84**: 131-7).

General information

Instructions to the printer. Words to be printed in lowercase italics should be indicated by one underline. Two underlines indicate small capitals, three indicate large capitals and four, italic capitals. A wavy underline indicates a word to be printed in bold type.

Headings in the text. Three possible grades are available, and may be indicated by the following letters of identification.

A **Results (bold)**
B *Lung function studies* (italics, ranged left)
C *Volume.* Large volumes... (italics, ranged left, text run on)

Symbols and abbreviations. In accordance with Editorial adoption of SI units, abbreviations and symbols should follow the conventions described in the booklet *Units, Symbols and Abbreviations. A Guide for Biological and Medical Editors and Authors* (D. N. Baron, ed.) (1988), published by and available from The Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE. Words for which abbreviations are not included should be written in full at first mention in the summary and again in the text and followed by the abbreviation in brackets. This will usually be in the form of large capitals without separating points.

Spelling, etc. British spelling should be used with 'z' rather than 's' spelling in, e.g. organize, organization.

Short communications

Authors are encouraged to submit short manuscripts suitable for rapid publication. In general, these should conform to the requirements outlined above, but with the following differences:

Format. Summary; Introduction (not headed); Methods and results; Comment.

Size. Not more than 6 references, 1 table or 1 figure, one-and-a-half pages of printed text (1200 words).

Correspondence

Each issue of the journal will contain correspondence. Correspondence arising from papers in a recent issue is published without delay, and for this reason, will be given priority over that pertaining to original research. The Editor may change, delete or modify in any way all items of correspondence.

All communications designed for publication should be submitted on a separate page in letter quality heavy type (not dot matrix), double-spaced, on one side only of the paper, with a wide margin. Contributors should send three copies of all correspondence to the editor and retain a copy in case of loss. Correspondence must also be submitted on disk. All authors must sign the accompanying submission letter. A fax number and an E-mail address should be supplied.

Proofs

These should be corrected and returned to the publisher by post or fax within 48 h of receipt. Overseas contributors may fax a copy of the proofs to the publisher but should return their proofs by air mail also.

Reprints

Corresponding authors will receive a copy of the journal in which their article appears. Offprints can be supplied if application is made on the order form attached to the proofs. The order form should be returned with the proofs.

IMPORTANT NOTICE TO AUTHORS

Electronic submission of new manuscripts to the British Journal of Anaesthesia. Please note that, from January 2003, the Editorial team requests that all new manuscripts (excluding Letters to the Editor and Book Reviews), be submitted electronically to the *British Journal of Anaesthesia* web site at: http://bja.manuscriptcentral.com

Clear instructions for submission of new manuscripts are available on this web site. If these instructions are not adhered to, difficulty will be experienced in submitting new articles. For an interim period, manuscripts may also be submitted as hard copy to the Editor-in-Chief's office. It is envisaged, however, that this arrangement will be discontinued by the end of 2003.

ANESTHESIA & ANALGESIA

Journal of the International Anesthesia Research Society, the Society of Cardiovascular Anesthesiologists, the Society for Pediatric Anesthesia, the Society for Ambulatory Anesthesia, the International Society for Anaesthetic Pharmacology, and the Society for Technology in Anesthesia

EDITORIAL

509 Anesthetic-Induced Immobility

CARDIOVASCULAR ANESTHESIA
(Society of Cardiovascular Anesthesiologists)

512 Utility of Preoperative Dobutamine Stress Echocardiograms
517 Intraoperative Low-Dose Dobutamine Echocardiography
524 Mitral Propagation Velocity and Coronary Artery Bypass Grafting
531 Ketamine, Cardiopulmonary Bypass, and Neutrophil Activation
537 Ventricular Arrhythmias After Thoracic Surgery
544 HES 130/0.4 in Renal Impairment
552 Irrigation Associated ST-Segment Increase (Case Report)
555 Anesthesia and Catecholaminergic Polymorphic Ventricular Tachycardia (Case Report)
558 TEE-Associated Airway Obstruction (Case Report)
561 TEE Probe Via Endoscopy Mask (Case Report)
564 Subclavian Artery Injury (Case Report)
567 Pericardial Hematoma Versus Intracavity Mass (Case Report)
570 Pneumothorax During One-Lung Ventilation (Case Report)

ANESTHETIC PHARMACOLOGY
(International Society for Anaesthetic Pharmacology)

573 Alkanes Inhibit Neuronal Nicotonic Receptors
578 Anesthetics/Glycine Receptor Mutant Mice
583 Isoflurane and Adhesion Molecules
588 Kinetic-Dynamics of Rocuronium in Myasthenia Gravis
597 Propofol-Sufentanil Target Controlled Infusion
606 $MgSO_4$ and Propofol Pain (Brief Report)
609 Design of MAC Studies (Medical Intelligence)

PEDIATRIC ANESTHESIA
(Society for Pediatric Anesthesia)

615 Intubation During Sevoflurane and No Relaxant Administration
621 Colobronchial Fistula in a Pediatric Patient (Case Report)
624 Pediatric Thoracic Nailgun Injury (Case Report)

AMBULATORY ANESTHESIA
(Society for Ambulatory Anesthesia)

627 Pain After Ambulatory Surgery
635 A Novel Portable Intravenous Device (Technical Communication)

TECHNOLOGY, COMPUTING, AND SIMULATION

639 Bispectral Index in Target or Manually Controlled Infusion of Propofol
645 Acoustic Prediction of Difficult Airway
650 CO Formation and CO_2 Absorption in Absorbents
656 Scavenging Hood to Reduce Gas Contamination

PAIN MEDICINE

661 Intrathecal Magnesium Prolongs Fentanyl Analgesia
667 Effects of Parecoxib on the Response to Midazolam
674 Spinal Analgesic Combinations (Review Article)

CRITICAL CARE AND TRAUMA

716 Predicting Defibrillation Outcome
723 Acupressure, Pain, and Trauma

OBSTETRIC ANESTHESIA

728 Addition of Clonidine to Ropivacaine for Labor
735 Clonidine and Ropivacaine Minimum Local Analgesic Concentration
741 Postcesarean Analgesia on Day 2

REGIONAL ANESTHESIA

746 Cervical Block for Thyroid Surgery
751 Phenylephrine and Spinal Anesthesia-Induced Hypotension
757 Hypobaric Lidocaine and Transient Neurologic Syndrome (Case Report)
760 Shearing of a Peripheral Nerve Catheter (Case Report)
762 Paresthesias with Nerve Stimulator (Case Report)

GENERAL ARTICLES

764 Jet Ventilation and Laryngotracheal Stenosis
770 Proseal™ Versus Laryngeal Tube
777 Myoclonic Seizure, PACU, Laminectomy (Case Report)
780 LETTERS TO THE EDITOR
788 BOOK AND MULTIMEDIA REVIEWS

Visit
SPA Webs
ww

ISSN 0003-2999 Volume 95, Number 3, September 2002
www.anesthesia-analgesia.org

OXFORD JOURNALS

Medicine

www.oupjournals.org/medicine/?f2

Oxford University Press publishes some of the most respected and highly-cited medical journals in the world including:

BJA: British Journal of Anaesthesia

Human Reproduction

Journal of Antimicrobial Chemotherapy

Nephrology Dialysis Transplantation

Rheumatology

➲ **FULL TEXT** *now online*

If you are a current print subscriber (institutional or personal), visit **www3.oup.co.uk/Register/?f2** to activate your online access.

➲ **FREE @ the web site:**

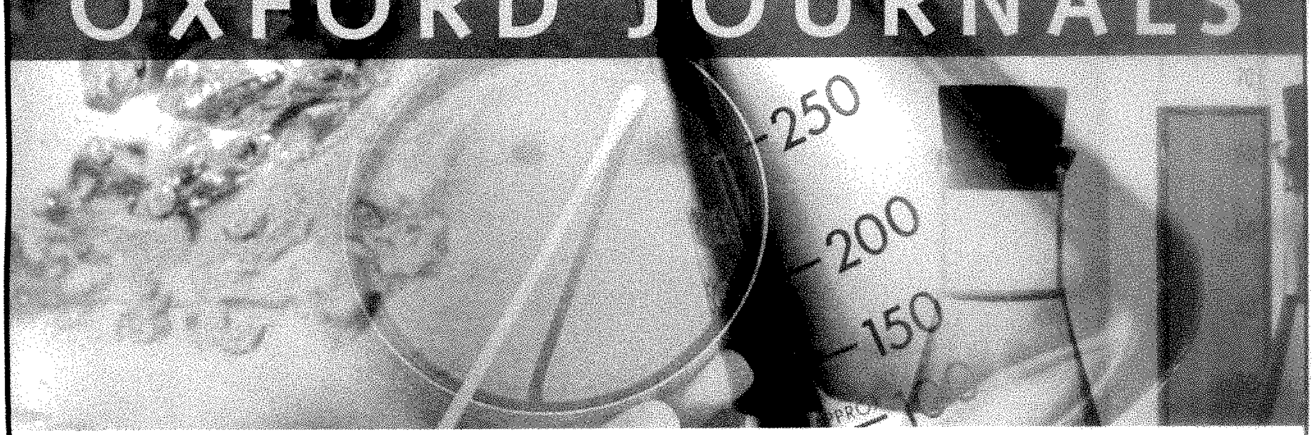
- **tables of contents by e-mail**
- **sample issues**
- **abstracts and tables of contents**
- **instructions to authors**

To subscribe to the above journals, visit the web site @
www.oupjournals.org/medicine/?f2

For further information please contact:
Journals Dept. • E-mail: jnls.cust.serv@oup.co.uk
Tel: +44 1865 267907 • Fax: +44 1865 267835
In the Americas, please contact:
Journals Dept. • E-mail: jnlorders@oup-usa.org
Tel: +1 800 852 7323 (USA/Canada) or +1 919 677 0977
(outside USA/Canada) • Fax: +1 919 677 1714

OXFORD
UNIVERSITY PRESS

OXFORD JOURNALS



BJA CEPD Reviews

www.oupjournals.org/list/bjarev/?f2

Editor-in-Chief: David J Rowbotham

BJA CEPD Reviews is a joint venture of the British Journal of Anaesthesia and The Royal College of Anaesthetists in collaboration with the Intensive Care Society and Pain Society.

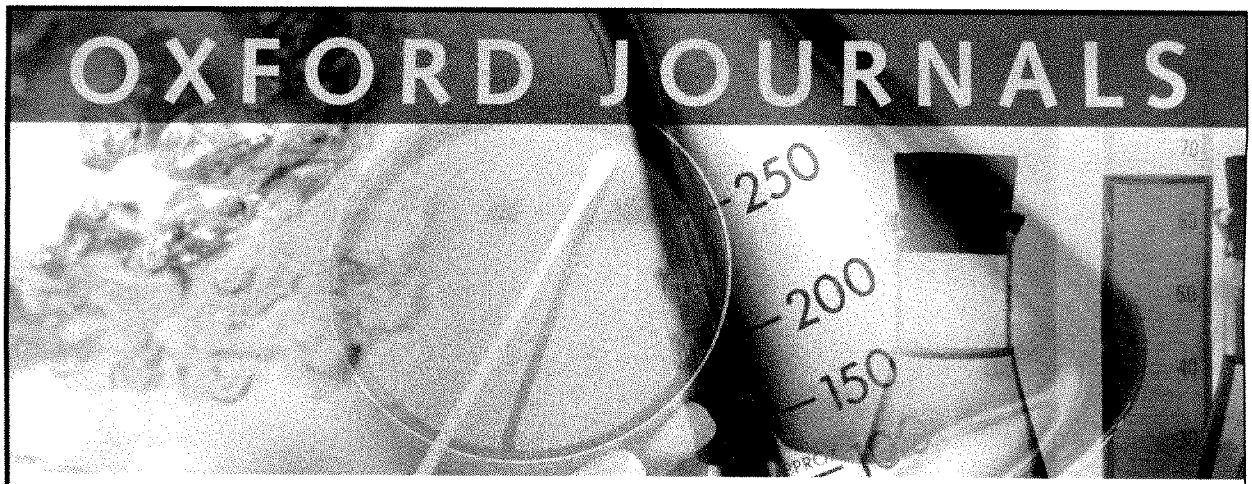
The purpose of ***BJA CEPD Reviews*** is the publication of material to support the continuous medical education and professional development of specialists in anaesthesia, critical care medicine and pain

To subscribe, visit the web site @
www.oupjournals.org/list/bjarev/?f2

For further information please contact:
Journals Dept. • E-mail: jnls.cust.serv@oup.co.uk
Tel: +44 1865 267907 • Fax: +44 1865 267835

In the Americas, please contact:
Journals Dept. • E-mail: jnlorders@oup-usa.org
Tel: +1 800 852 7323 (USA/Canada) or +1 919 677 0977
(outside USA/Canada) • Fax: +1 919 677 1714

OXFORD
UNIVERSITY PRESS



OXFORD JOURNALS

QJM - An International Journal of Medicine

Editor: Dr. Christopher N. Martyn

www.qjmed.oupjournals.org/?f2

QJM is a long-established, leading general medical journal. It focuses on internal medicine and publishes peer-reviewed articles which promote medical science and practice.

7 reasons to publish in QJM

1 Impact factor of 2.25
2 Rapid publication - about 10 weeks post acceptance
3 Opportunity for in-depth articles and reviews
4 Influential readership that includes a wide range of specialists
5 Online manuscript submissions from 2002 - e-mail submissions already accepted
6 Wide usage of QJM online and extensive links ensure a high profile for all papers
7 Inclusion in all major indexing/abstracting services

➲ FULL TEXT *now online*

If you are a current print subscriber (institutional or personal), visit **www3.oup.co.uk/Register/?f2** to activate your online access.

➲ FREE @ the web site:

- tables of contents by e-mail
- sample issue
- abstracts and tables of contents
- instructions to authors

To subscribe, visit the web site @
www.qjmed.oupjournals.org/?f2

For further information please contact:
Journals Dept. • E-mail: jnls.cust.serv@oup.co.uk
Tel: +44 1865 267907 • Fax: +44 1865 267835
In the Americas, please contact:
Journals Dept. • E-mail: jnlorders@oup-usa.org
Tel: +1 800 852 7323 (USA/Canada) or +1 919 677 0977
(outside USA/Canada) • Fax: +1 919 677 1714

OXFORD
UNIVERSITY PRESS

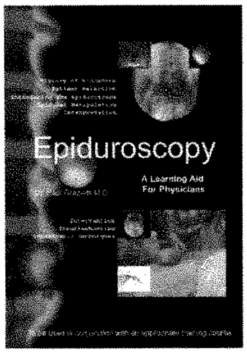
EPIDUROSCOPY

A learning aid for physicians

60 minutes of high quality digital video on DVD format

Includes sections on

- History of procedure
- Patient selection
- Introducing the scope
- Manipulating the scope in the epidural space
- Interpreting findings
- Interventional techniques
- Troubleshooting
- Anaesthetic considerations



Produced by Dr Paul Graziotti MBBS FFARACS FFARCS FFPMANZCA, Pain Management Physician

The perfect refresher tool for beginning and established practitioners.

Available for purchase at www.ipmt.net

14th South West Thames
Anaesthesia Update

27-31 January 2003
Belle Plagne, French Alps

Open to all Anaesthetists

The Scientific Programme will include lectures, and discussions on:

- Acute and Chronic Pain
- Paediatric Update
- Day Case Anaesthesia
- Obstetric Anaesthesia
- Neurology and Anaesthesia
- ITU and Relevant Medical Topics
- Cardiothoracic topics
- Radiology for Anaesthetist
- New Drugs Update
- Training &Education
- Anaesthetic Audit
- Free papers
- Panel Discussions
- Workshops

Guest Speakers
Videos on New Equipment, Drugs and Techniques
Anaesthetists in training presenting papers are eligible for prizes.
Deadline for abstracts: December 9th 2002
This Meeting is approved for CME purposes

For further details, please contact:
Dr J.B. Liban
Department of Anaesthesia
St George's Hospital
Blackshaw Road,
London SW17 0QT
Fax: +44 (0)20 8725 3135
Tel: +44 (0)20 8725 0018
email: liban@mailbox.co.uk

www.doctorsupdates.com
medical education in a perfect location

OXFORD JOURNALS
ADVERTISING

To advertise in this publication contact

PRC
ASSOCIATES

Advertisement Managers

THE ANNEXE, FITZNELLS MANOR
CHESSINGTON ROAD, EWELL VILLAGE, SURREY KT17 1TF, UK
TELEPHONE: +44 (0)20 8786 7376 FAX: +44 (0)20 8786 7262
EMAIL: mail@prcassoc.co.uk

Anaesthesia Pain Fellowship
McMaster University, Hamilton, Canada

Applications are invited to an Anaesthesia Pain Fellowship at McMaster University. Referrals in Pain Clinics from Central-South and Northwestern regions, Province of Ontario. Annual visits 10,000 - 12,000. Services include acupuncture, nerve blocks, implantable nerve stimulators, etc.

DEADLINE FOR APPLICATIONS:
OCTOBER 30, 2002

Further information is available on the website:
www.fhs.mcmaster.ca/anaesthesia/education
or from:

Mrs. Mary Gahagan, Office of the Chair,
Department of Anaesthesia,
McMaster University, 1200 Main St. W.,
Hamilton, Ontario, Canada L8N 3Z5
Tel: 905-521-2100 Ext. 75166
Fax: 905-523-1224
e-mail: gahaganm@mcmaster.ca

Queen's
UNIVERSITY

12th Annual

WHISTLER WINTER ANESTHESIA
Refresher Course & Review

February 22 – February 28, 2003

Whistler, British Columbia, Canada

22 hours CME credits
Poster presentations

For information:

Whistler Winter Anesthesia Meeting
Department of Anesthesiology
Kingston General Hospital
76 Stuart Street
Kingston, Ontario, Canada, K7L 2V7

Voice Mail: (613) 549-6666 Ext. 3276
Fax: (613) 548-1392
E-mail: wwanesth@kgh.kari.net
Web Site: http://meds.queensu.ca/whistler

Washington
University in St. Louis
SCHOOL OF MEDICINE

CHIEF OF NEUROLOGIC ANESTHESIA

The Department of Anesthesiology at Washington University School of Medicine is seeking an experienced academic anesthesiologist to head the Section of Neurologic Anesthesia and direct the clinical and academic activities of the service. The service provides anesthesia coverage for approximately 1,600 cases per year. A strong multidisciplinary integrated approach with the neurosurgery, neuroradiology and neurointensive care services is already established. The infrastructure for clinical and outcome research is in place. The faculty appointment is at the rank of Associate Professor or Professor and is commensurate with the candidate's credentials. Salary and benefits are competitive. Candidates interested in this position should send their CV to:

René Tempelhoff, MD
Chair of Search Committee
Department of Anesthesiology
Washington University School of Medicine
660 S. Euclid Avenue, Campus Box 8054
St. Louis, MO 63110.
Telephone: (314) 362-2330
E-mail: tempelhr@msnotes.wustl.edu.

TWO DAY COURSE ON
TRANSOESOPHAGEAL ECHOCARDIOGRAPHY
Thursday 6th - Friday 7th March 2003
St George's Hospital, London, United Kingdom

St George's Hospital Medical School
University of London

Course Directors:
Dr Stephen Brecker and Mr Graham Leech
with **International Faculty**

Topics will include:
Live ASD Closure.-.Live Anatomy - Endocarditis
Prosthetic Valves - Intra-operative Applications
Congenital Disease - Aortic Dissection
Assessing Mitral Valve Anatomy
TOE in Anaesthesia - Ventricular function

For further details please contact:
Dr S Brecker, Cardiology
St George's Hospital, Blackshaw Road,
London SW17 0QT
Tel: +44 (0)20-8725-1390 Fax: +44 (0)20-8725-0211
e-mail: cmurphy@sghms.ac.uk

BJA

International Journal of Anaesthesia

Volume 89 Number 5 November 2002

EDITORIAL

683 I. Live and let die? A structured approach to decision-making about resuscitation
P. Levack

CLINICAL INVESTIGATIONS

687 Cerebral haemodynamics in pregnancy and pre-eclampsia as assessed by transcranial Doppler ultrasonography
R. W. Sherman, R. A. Bowie, M. M. E. Henfrey, R. P. Mahajan and D. Bogod

693 Fluoride excretion in children after sevoflurane anaesthesia
C. Lejus, C. Le Roux, E. Legendre, M. Renaudin, H. L. Boiteau and M. Pinaud

697 Is morphine-induced sedation synonymous with analgesia during intravenous morphine titration?
X. Paqueron, A. Lumbroso, P. Mergoni, F. Aubrun, O. Langeron, P. Coriat and B. Riou

702 Spinal anaesthesia: comparison of plain ropivacaine 5 mg ml^{-1} with bupivacaine 5 mg ml^{-1} for major orthopaedic surgery
D. A. McNamee, A. M. McClelland, S. Scott, K. R. Milligan, L. Westman and U. Gustafsson

707 Paediatric regional anaesthesia, a survey of practice in the United Kingdom
J. C. Sanders

711 Efficacy of intravenous magnesium in neuropathic pain
S. Brill, P. M. Sedgwick, W. Hamann and P. P. di Vadi

715 Platelet function point-of-care tests in post-bypass cardiac surgery: are they relevant?
F. Forestier, A. Coiffic, C. Mouton, D. Ekouevi, G. Chêne and G. Janvier

722 Effects of a new modified, balanced hydroxyethyl starch preparation (Hextend®) on measures of coagulation
J. Boldt, G. Haisch, S. Suttner, B. Kumle and A. Schellhaass

729 The laryngeal tube compared with the laryngeal mask: insertion, gas leak pressure and gastric insufflation
T. Asai, A. Kawashima, I. Hidaka and S. Kawachi

733 Fibreoptic tracheal intubation after placement of the laryngeal tube
H. V. Genzwuerker, T. Vollmer and K. Ellinger

LABORATORY INVESTIGATION

739 Neuroprotective and neurotoxic properties of the 'inert' gas, xenon
D. Ma, S. Wilhelm, M. Maze and N. P. Franks

REVIEW ARTICLE

747 Preoperative evaluation of patients with, or at risk of, coronary artery disease undergoing non-cardiac surgery
P.-G. Chassot, A. Delabays and D. R. Spahn

SHORT COMMUNICATIONS

760 Patient preferences for immediate postoperative recovery
L. H. J. Eberhart, A. M. Morin, H. Wulf and G. Geldner

762 Effect of diclofenac on cerebral blood flow velocity in patients with supratentorial tumours
S. J. Jones and J. Dinsmore

764 Sevoflurane and propofol decrease intraocular pressure equally during non-ophthalmic surgery and recovery
S. Sator-Katzenschlager, E. Deusch, S. Dolezal, A. Michalek-Sauberer, R. Grubmüller, G. Heinze and A. Wedrich

766 Atracurium is associated with postoperative residual curarization
C. McCaul, É. Tobin, J. F. Boylan and A. J. McShane

769 Effects of prolonged head-down tilt on internal jugular vein cross-sectional area
S. J. Schreiber, U. K. W. Lambert, F. Doepp and J. M. Valdueza

772 Posture used by anaesthetists during laryngoscopy
J. D. Walker

CASE REPORTS

775 Air embolism: diagnosis with single-photon emission tomography and successful hyperbaric oxygen therapy
L. Droghetti, M. Giganti, A. Memmo and R. Zatelli

778 Epidural abscess complicating insertion of epidural catheters
J. M. G. Phillips, J. C. Stedeford, E. Hartsilver and C. Roberts

782 Unexplained fitting in three parturients suffering from postdural puncture headache
C. D. Oliver, S. A. White

786 Anaesthesia in an adult with Rubenstein–Taybi syndrome using the ProSeal laryngeal mask airway
S. J. Twigg and T. M. Cook

788 General anaesthesia in a patient with Brugada syndrome
C. J. Edge, D. J. Blackman, K. Gupta and M. Sainsbury

COMMENTARY

792 Preoperative use of herbal medicines: a patient survey
C. M. Skinner and J. Rangasami

796 CORRESPONDENCE

802 BOOK REVIEWS

Joint Meeting of the

European Society of Anaesthesiologists

European Academy of Anaesthesiology

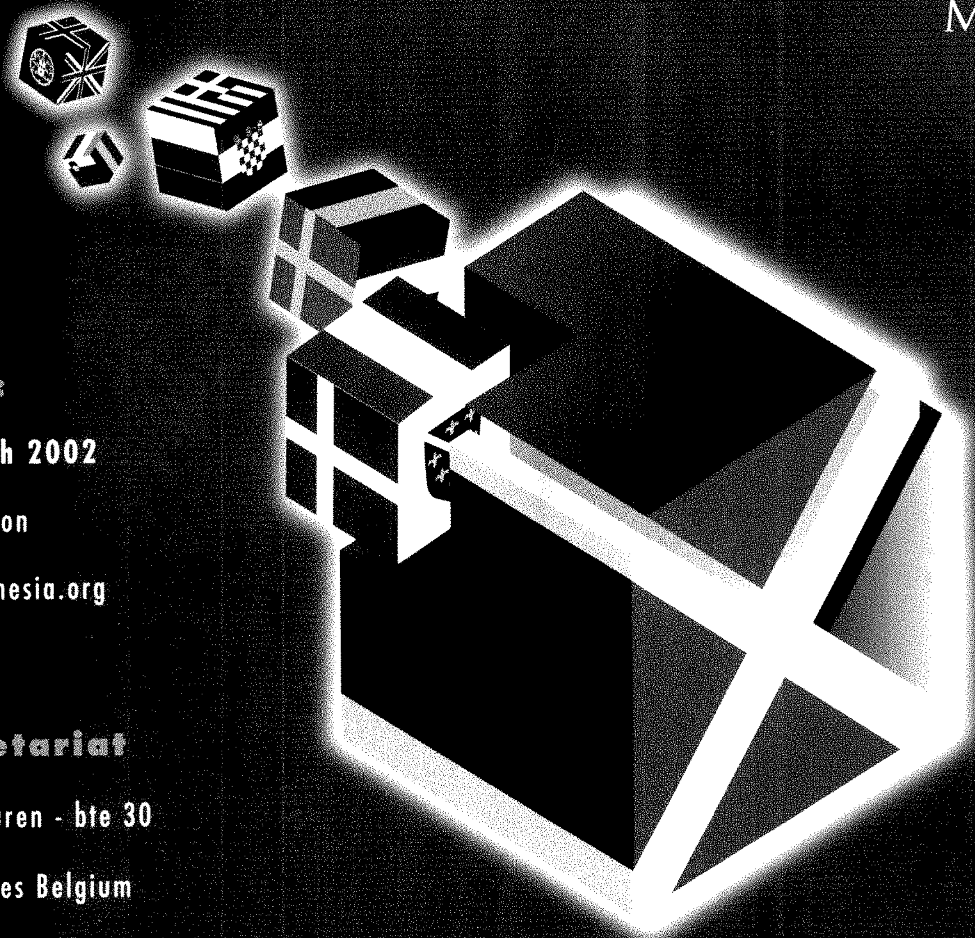
Confederation of European National Societies of Anaesthesiology

Association of Anaesthetists of Great Britain & Ireland

Glasgow Scotland

Euroanaesthesia 2003

MAY31-JUNE3



Deadline abstracts:

December 15th 2002

Online submission

www.euroanesthesia.org

ESA Secretariat

32 Av. de Tervuren - bte 30
B-1040 Bruxelles Belgium
Phone +32 (0) 2 743 32 90
Fax +32 (0) 2 743 32 98
E-mail: secretariat.esa@euronet.be

Symposia

Refresher Courses

Workshops

Industrial Symposia

& Exhibition

Free Presentations

AMA Category 1

CME Accreditation

Editorial Board

Editor-in-Chief

JENNIFER M. HUNTER, Professor of Anaesthesia, *University of Liverpool*

Editors

G. B. DRUMMOND, Senior Lecturer in Anaesthesia, *Royal Infirmary, Edinburgh*
P. M. HOPKINS, Professor of Anaesthesia, *University of Leeds*
D. G. LAMBERT, Reader in Anaesthetic Pharmacology, *University of Leicester*
D. J. ROWBOTHAM, Professor of Anaesthesia and Pain Management, *University of Leicester*

Board Members

F. BONNET, Professor of Anaesthesia, *Assistance Publique Hopitaux de Paris*
H. F. GALLEY, Senior Lecturer in Anaesthesia and Intensive Care, *University of Aberdeen*
G. M. HALL, Professor of Anaesthesia, *University of London*
S. J. HOWELL, Senior Lecturer in Anaesthesia, *University of Leeds*
P. HUTTON, President, *Royal College of Anaesthetists*
D. M. JUSTINS, Vice-president, *Royal College of Anaesthetists*
P. A. LONNQVIST, Associate Professor of Paediatric Anaesthesia and Intensive Care, *Lingrens Children's Hospital, Stockholm, Sweden*
R. P. MAHAJAN, Reader in Anaesthesia, *University of Nottingham*
R. D. MILLER, Professor of Anesthesia, *University of California, San Francisco*
I. POWER, Professor of Anaesthesia, Critical Care and Pain Medicine, *University of Edinburgh*
H.-J. PRIEBE, Professor of Anaesthesia, *University of Freiburg, Germany*
C. S. REILLY (Treasurer), Professor of Anaesthesia, *University of Sheffield*
J. W. SEAR, Professor of Anaesthesia, *University of Oxford*
P. J. SIMPSON, Vice-president, *Royal College of Anaesthetists*
G. SMITH (Chairman), Professor of Anaesthesia, *University of Leicester*
J. R. SNEYD, Professor of Anaesthesia, *University of Plymouth*
D. R. SPAHN, Professor of Anaesthesia, *University Hospital, Lausanne, Switzerland*
N. R. WEBSTER (Secretary), Professor of Anaesthesia, *University of Aberdeen*
J. A. W. WILDSMITH, Professor of Anaesthesia, *Ninewells Hospital and Medical School, Dundee*
J. D. YOUNG, Reader in Anaesthesia, *Radcliffe Infirmary, Oxford*

International Board Members

F. CARLI, Wesley Bourne Professor and Chairman, Department of Anesthesia, *McGill University, Montreal, Canada*
K. HIROTA, Department of Anesthesiology, *University of Hirosaki, Japan*

Assistant Editors

R. S. JONES, Emeritus Professor of Veterinary Anaesthesia, *University of Liverpool*
B. V. S. MURTHY, Consultant Anaesthetist, *Royal Liverpool University Hospital*

Production Staff

E. GOODING, Senior Production Editor, *Oxford University Press*
H. J. LAMB, Production Editor, *Oxford University Press*
G. G. R. T. MUCKLOW, Editorial Assistant, *Oxford University Press*
Please visit the Journals's World Wide Web site at http://bja.oupjournals.org

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

General Information

Subscriptions

All Fellows of the College, world-wide, should notify changes of address directly to the Royal College of Anaesthetists.

An annual subscription to *BJA* comprises 12 issues (two volumes of 6 issues), with Author and Subject Indexes. Subscriptions are entered on a calendar year basis only. Please add local sales tax to the prices quoted. Prices include postage by surface mail, or for subscribers in the USA and Canada by Airfreight, or in Japan, Australia, New Zealand, and India by Air Speeded Post. Airmail rates are available on request.

Annual subscription rate 2002

Full text print version of the *BJA*

Full rate (institutions and individuals): UK and Europe £255, Rest of World US$400

Trainees: UK and Europe £120, Rest of World US$190

ESA/EACTA/EAA/ESRA/JSA/IARS members: UK and Europe £120, Rest of the World US$190

Single issue: UK and Europe £27, Rest of World US$38

Orders

Orders and payments from, or on behalf of, subscribers in the various geographical areas shown below should be sent to the office indicated. Payment may be made by the following methods: cheque (made payable to Oxford University Press); National Girobank (Account 500 1056); credit card (Mastercard, Visa, American Express); UNESCO coupons; direct debit (please ask for details). Bankers: Barclays Bank plc, PO Box 333, Oxford, UK; Code 20-65-18; Account 00715654.

The Americas: Oxford University Press Inc., 2001 Evans Road, Cary, NC 27513, USA.

Japan: available from the following agents:

Kinokuniya Company Ltd, Journal Department, PO Box 55, Chitose, Tokyo, 156 Japan.
Maruzen Company Ltd, Journal Division, PO Box 5050, Tokyo International, 100-31 Japan.
Usaco Corporation, 13-12 Shimbashi 1-chome, Minato-ku, Tokyo, 105 Japan.

Rest of the world: Oxford University Press, Journals Subscriptions Department, Great Clarendon Street, Oxford OX2 6DP, UK. Tel +44 (0)1865 267907; Fax: +44 (0)1865 267485; E-mail: jnl.orders@oup.co.uk

Please address orders and enquiries about availability as follows: *For current volume and back numbers from Vol. 82 onwards* to Oxford University Press. *For Vols 1-81* to Periodicals Service Company, 11 Main Street, Germantown, NY 12526, USA.
Tel: +1 (518) 537 4700; Fax: +1 (518) 537 5899.

Advertising

Advertising enquiries should be addressed to Peter Carpenter, PRC Associates, The Annexe, Fitznells Manor, Chessington Road, Ewell Village, Surrey KT17 1TF, UK. Tel: +44 (0)20 8786 7376; Fax: +44 (0)20 8786 7262; E-mail: mail@prcassoc.co.uk

© *The Board of Management and Trustees of the British Journal of Anaesthesia 2002*

All rights reserved; no part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise without the prior written permission of the *British Journal of Anaesthesia*, requests for which should be addressed to the Publisher, or a licence permitting restricted copying issued in the UK by the Copyright Licensing Agency Ltd, 90 Tottenham Court Road, London W1P 9HE, or in the USA by the Copyright Clearance Center, 222 Rosewood Drive, Danvers, MA 01923. For those in the US/Canada not registered with CCC, articles can be obtained by fax in 48 hours by calling: WISE for MedicineTM 1-800-667-WISE.

British Journal of Anaesthesia (ISSN 0007-0912) is published monthly by Oxford University Press, Oxford, UK. Annual subscription price is US$400. *British Journal of Anaesthesia* is distributed by Mercury International, 365 Blair Road, Avenel, NJ 07001, USA. Periodicals postage paid at Rahway, New Jersey, and additional entry points.

US Postmaster: send address changes to *British Journal of Anaesthesia*, c/o Mercury International, 365 Blair Road, Avenel, NJ 07001, USA.

Disclaimer

Whilst every effort is made by the publishers and editorial committee to see that no inaccurate or misleading data, opinions or statements appear in this Journal, they wish to make it clear that the data and opinions appearing in the articles and advertisements herein are the responsibility of the contributor or advertiser concerned. Accordingly, the publisher and the editorial committee and their respective employees, officers and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinions or statements. While every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described within this Journal, should only be followed in conjunction with the drug manufacturer's own published literature.

Printed by Information Press Ltd, Oxford, UK.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

MEDICA®

Visit our booth
November 20.–23., 2002
Düsseldorf, Germany
Hall 11 / 11 J 39

The Fabius GS combines superior performance with ease of use. An electronically controlled piston ventilator provides both volume control and true pressure control ventilation modes without weight or age restrictions. The revolutionary user interface is simple, intuitive and allows the electronic capture of fresh gas data for inclusion in a perioperative information system. Integrated equipment mounting rails and a unique CPU storage area allow the user to create their own tailor-made ergonomic workstation.

Fabius GS is one of *three* pillars of innovation that mark a revolutionary new chapter in Dräger Medical's anesthesia device technology.

The essence of anesthesia.

Dräger
MEDICAL

Editorial Notices

Important Notice to Authors

Electronic Submission of New Manuscripts to *The British Journal of Anaesthesia*

Please note that, from January 2003, the Editorial team requests that all new manuscripts (excluding Letters to the Editor and Book Reviews) be submitted electronically to the *British Journal of Anaesthesia* web site at: http://bja.manuscriptcentral.com

Clear instructions for submission of new manuscripts are available on this web site. If these instructions are not adhered to, difficulty will be experienced in submitting new articles. For an interim period, manuscripts may also be submitted as hard copy to the Editor-in-Chief's office. It is envisaged, however, that this arrangement will be discontinued by the end of 2003.

Jennifer M. Hunter
Editor-in-Chief

Royal Medical Benevolent Fund

President's Christmas Message for 2002

Readers of the *British Journal of Anaesthesia*, in recent years, have been generous in their response to the Christmas Appeal on behalf of the Royal Medical Benevolent Fund.

As newly elected President of the Fund, I have seen the support it gives to those doctors and their dependants who are less fortunate than ourselves. Whether as a result of health problems, an unexpected family tragedy, or other reasons, there are all too many doctors and their families who are in great need—and never is that need more evident than at Christmas.

Since 1870, the President of the Fund has made a Christmas appeal to those doctors in happier circumstances to help provide a gift, or more usually, a little money. This helps to transform a cheerless Christmas into a very happy one, especially when children are involved, as they frequently are. Last year's appeal raised some £74,000. Let us try to exceed this and establish a new record. Please consider sending a donation, preferably using gift aid, and help brighten Christmas 2002 for many needy colleagues and their dependants. Contributions marked 'Christmas Appeal' may be sent to the RMBF, 24 King's Road, Wimbledon, London SW19 8QN or to the Treasury of your local guild of this Fund. Thank you.

To those of you who may already have contributed—a very warm thank you.

Royal Medical Benevolent Fund

Are you a current or very recently retired doctor? Would you like to help colleagues less fortunate than yourself? Our recent cases include doctors who have suffered strokes, cancer, multiple sclerosis, paralysis after serious road accidents, blindness, schizophrenia, manic depression, dependency and the suicide of a partner. A growing number are junior doctors with limited pension entitlement and insurance cover.

Do you have a few hours to help?

Medical Liaison Officer

The aim is to ensure doctors and their families in your area are aware of the financial help which may be available from the RMBF in time of crisis, and in particular to:

- Liaise with local hospitals, medical centres, medical societies and associations, to seek to ensure that doctors and their families are aware of the type of help the Fund may be able to provide.
- To provide information about the RMBF to any colleagues and their dependants likely to need assistance and to advise the Fund where appropriate.
- To advise the Fund of any planned medical conferences, exhibitions or meetings in your area where it might be possible for the RMBF to be represented.

We need career grade doctors who are currently practising or very recently retired (i.e. within the last two years), with good contacts within the medical world and able to commit on average a couple of hours a week to help the Fund.

For further information about becoming a volunteer Medical Liaison Officer for the Fund, please contact: Royal Medical Benevolent Fund, 24 King's Road, Wimbledon, London SW19 8QN. Tel: +44 (0)208 540 9194; E-mail: info@rmbf.org

Help!

Have you had a patient showing signs of hypoxic brain damage when the Holmann laser was used, or urea renal

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

MEDICA®

Visit our booth
November 20.–23., 2002
Düsseldorf, Germany
Hall 11 / 11 J 39

Primus, Dräger Medical's next-generation anesthesia workstation, is designed to be your personal anesthesia assistant in the most demanding operations and everyday clinical routine. And like every good assistant, Primus supports your decision-making for improved efficiency in low-flow delivery and ventilation. Primus sets new standards in perioperative therapy with its new, innovative intensive care ventilator performance. A modular design, open-platform architecture and optional upgrade packages ensure you get a customized personal assistant to meet your specific requirements, e.g. with the patient monitoring system of your choice. So you can enjoy optimized processes in the perioperative environment.

Primus is one of *three* pillars of innovation that mark a revolutionary new chapter in Dräger Medical's anesthesia device technology.

The essence of anesthesia.

Dräger
MEDICAL

NEW for the relief of pain a

RCOXIA® (etoricoxib)
BRIDGED PRODUCT INFORMATION

fer to Summary of Product Characteristics before prescribing.

ESENTATION

lets: 60 mg, 90 mg and 120 mg tablets each containing 60 mg, 90 mg or 120 mg of etoricoxib pectively.

ES

nptomatic relief of osteoarthritis, rheumatoid arthritis (RA) and the pain and signs of lammation associated with acute gouty arthritis.

SAGE AND ADMINISTRATION

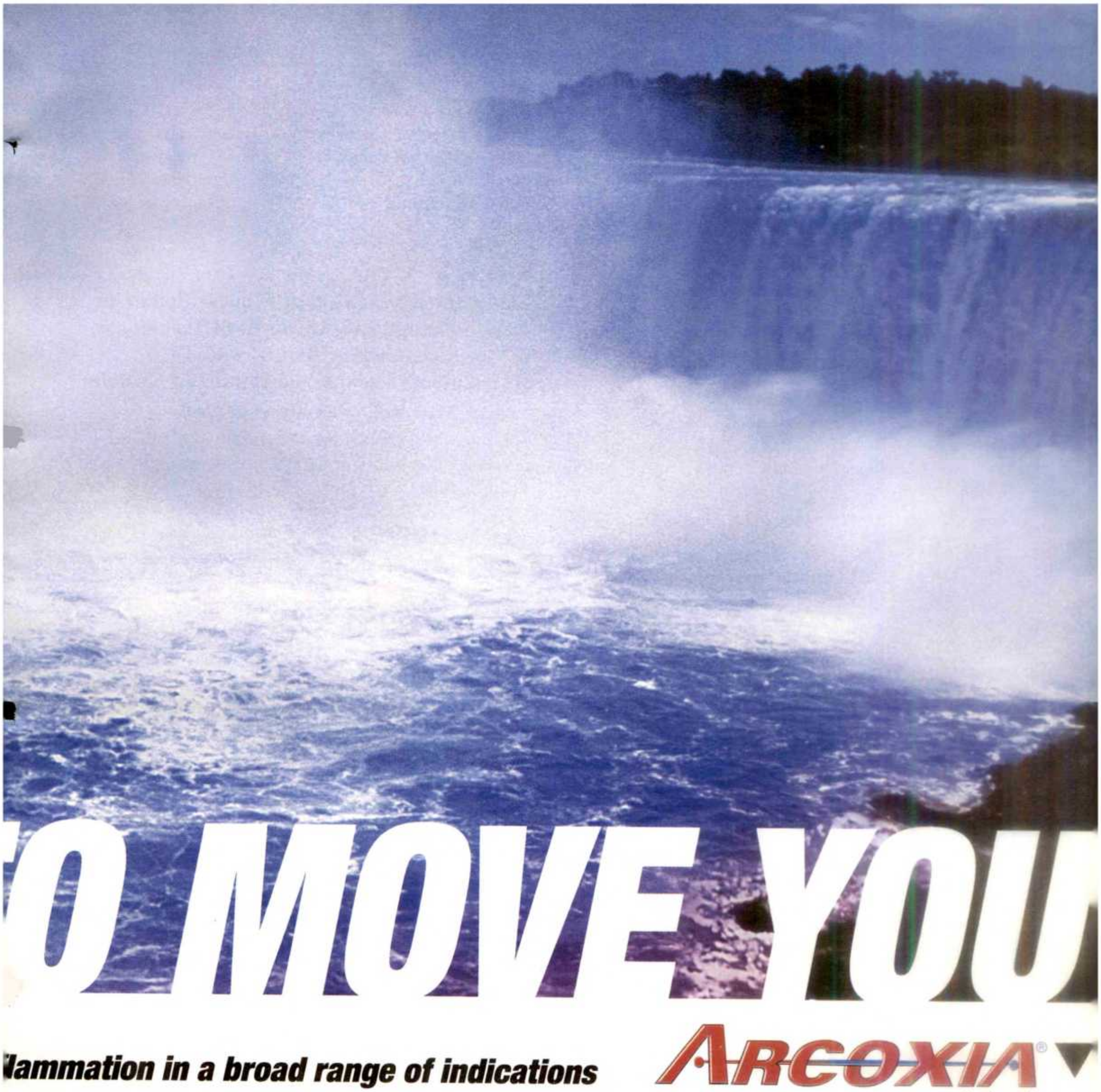
ce orally with or without food. Onset of action may be faster when administered without d, and should be considered when rapid relief is needed. *Osteoarthritis*: 60 mg once daily. *eumatoid arthritis*: 90 mg once daily. *Acute gouty arthritis*: 120 mg once daily for the acute nptomatic period only. Each dose above is the maximum recommended dose for each idition. *Renal insufficiency*: No dosage adjustment necessary for patients with creatinine arance ≥30 ml/min. *Hepatic insufficiency*: *mild* (Child-Pugh score 5-6): do not exceed a se of 60 mg; *moderate* (Child-Pugh score 7-9): **do not exceed 60 mg every other day**.

NTRA-INDICATIONS

persensitivity to any component of this product. Active peptic ulceration or gastro-intestinal) bleeding. Severe hepatic dysfunction (Child-Pugh score >9). Estimated creatinine clearance 0 ml/min. Patients who have developed signs of asthma, acute rhinitis, nasal polyps, ioneurotic oedema or urticaria after aspirin or other NSAIDs. Pregnancy and lactation. Children and adolescents under 16 years of age. Inflammatory bowel disease. Severe congestive heart failure.

PRECAUTIONS

Cardiovascular: COX-2-selective inhibitors are not a substitute for aspirin for cardiovascular prophylaxis due to their lack of effect on platelets. Because etoricoxib does not inhibit platelet aggregation, do not discontinue antiplatelet therapies and if indicated, consider them in patients at risk for or with a history of cardiovascular or other thrombotic events. Exercise caution in patients with a medical history of ischaemic heart disease. Take appropriate measures and consider discontinuing etoricoxib therapy if there is clinical evidence of symptomatic deterioration in the condition of these patients. Lack of antiplatelet activity should also be considered in patients with a history of cerebrovascular disease. *Renal effects*: Consider monitoring renal function in patients with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis. *Fluid retention, oedema and hypertension*: Exercise caution in patients with a history of cardiac failure, left ventricular dysfunction, or hypertension and pre-existing oedema from any other reason, as fluid retention and oedema have been observed in patients taking etoricoxib. Take appropriate measures, including discontinuation of etoricoxib where there is clinical evidence of deterioration in the condition of these patients. *Gastro-intestinal effects*: In clinical studies, some patients treated with etoricoxib, developed perforations, ulcers or bleeds (PUBs). Independent of treatment, patients with a history of GI perforation, ulcers and bleeding and those aged greater than 65 years are known to be at higher risk of a PUB. *Hepatic effects*: Elevations of ALT and/or AST (>3 times the upper limit of normal) have been reported in approximately 1% of patients treated in trials with etoricoxib 60 mg and 90 mg for up to one year. Monitor any patient with symptoms/signs of liver dysfunction or in whom an abnormal liver function test has occurred. Discontinue etoricoxib if signs of hepa insufficiency occur, or if persistently abnormal liver function tests (3 times the upper limi normal) are detected. *General*: Maintain appropriate medical supervision when treating elderly and patients with renal, hepatic or cardiac dysfunction with etoricoxib. Use caution w initiating treatment in patients with considerable dehydration. Rehydrate patients prior to start therapy with etoricoxib. Etoricoxib may mask fever. Use of etoricoxib is not recommende women attempting to conceive. *Interactions (pharmacodynamic)*: *Oral anticoagulants*: clos monitor the prothrombin time INR when therapy with etoricoxib is initiated or the dose chan in patients receiving oral anticoagulants or similar agents, particularly in the first few d *Diuretics and ACE-inhibitors*: NSAIDS may reduce the effect of diuretics and antihypertens drugs. In some patients with compromised renal function, the co-administration of an A inhibitor and cyclo-oxygenase inhibitors may result in further deterioration of renal functi which is usually reversible. *Aspirin*: etoricoxib can be used concomitantly with aspirin at d used for cardiovascular prophylaxis (low dose aspirin). However, concomitant administra of low dose aspirin with etoricoxib may result in an increased rate of GI ulceration or o complications compared to use of etoricoxib alone. Concomitant administration of etoric with doses of aspirin **above** those for cardiovascular prophylaxis, or with other NSAIDS is recommended. *Cyclosporin/tacrolimus*: monitor renal function when etoricoxib and ei cyclosporin or tacrolimus is used in combination. *Interactions (pharmacokinetic) The e of etoricoxib on the pharmacokinetics of other drugs*: *Lithium*: the plasma concentratio lithium is increased by NSAIDS, therefore monitor and adjust blood lithium and lithium do if necessary. *Methotrexate*: adequate monitoring is recommended for methotrexate-rel toxicity when etoricoxib and methotrexate are administered concomitantly. *Oral Contracep (OC)*: Administration of etoricoxib 120 mg with an OC containing 35 mcg ethinyl estr



lammation in a broad range of indications

ARCOXIA®
etoricoxib

and 0.5 to 1 mg norethindrone for 21 days, either concomitantly or separated by 12 hours, eased the steady state $AUC_{0\text{-}24hr}$ of EE by 50 to 60%; however, norethindrone concentrations rally did not increase to a clinically relevant degree. Consider this increase in EE entration when selecting an oral contraceptive for use with etoricoxib. *Digoxin:* Patients gh risk of digoxin toxicity should be monitored for an increase in digoxin C_{max} when coxib and digoxin are administered concomitantly. *Effect of etoricoxib on drugs metabolised lfotransferases:* Etoricoxib is an inhibitor of human sulfotransferase activity, particularly T1E1 and has been shown to increase the serum concentrations of ethinyl estradiol. It may udent to exercise care when administering etoricoxib concurrently with other drugs primarily bolised by human sulfotransferases (e.g. oral salbutamol and minoxidil). *Effect of etoricoxib ugs metabolised by CYP isoenzymes:* Based on *in vitro* studies, etoricoxib is not expected ibit cytochromes P450 (CYP) 1A2, 2C9, 2C19, 2D6, 2E1 or 3A4. In a study in healthy cts, daily administration of etoricoxib 120 mg did not alter hepatic CYP3A4 activity as sed by the erythromycin breath test. *Effects of other drugs on the pharmacokinetics of oxib:* The main pathway of etoricoxib metabolism is dependent on CYP enzymes. CYP3A4 rs to contribute to the metabolism of etoricoxib *in vivo*. *Ketoconazole:* a potent inhibitor P3A4, dosed at 400 mg once a day for 11 days to healthy volunteers did not have any ally important effect on the single-dose pharmacokinetics of 60 mg etoricoxib (43% increase C). *Rifampicin:* Co-administration of etoricoxib with rifampicin, a potent inducer of CYP nes, produced a 65% decrease in etoricoxib plasma concentrations, an interaction which esult in recurrence of symptoms. *Antacids:* Antacids do not affect the pharmacokinetics ricoxib to a clinically relevant extent. *Pregnancy:* contra-indicated in the first, second ird trimesters of pregnancy. *Lactation:* contra-indicated.

SIDE EFFECTS

In clinical studies the following undesirable effects were reported at an incidence greater than placebo in patients with OA, RA or chronic low back pain treated with etoricoxib 60 mg or 90 mg for up to 12 weeks: *[Common (>1/100, <1/10) Uncommon (>1/1000, <1/100) Rare (>1/10,000, <1/1,000)]*

Infections and infestations: *Uncommon:* gastro-enteritis, upper respiratory infection, urinary tract infection. ***Immune system disorder:*** *Very rare:* drug hypersensitivity. ***Metabolism and nutrition disorders:*** *Uncommon:* appetite increase or decrease, oedema/fluid retention, weight gain. ***Psychiatric disorders:*** *Uncommon:* anxiety, depression, mental acuity decreased. ***Nervous system disorder:*** *Common:* dizziness, headache. *Uncommon:* dysgeusia, insomnia, paraesthesia/hypaesthesia, somnolence. ***Eye disorders:*** *Uncommon:* blurred vision. ***Ear and labyrinth disorders:*** *Uncommon:* tinnitus. ***Cardiac disorders:*** *Uncommon:* congestive heart failure, non-specific ECG changes. *Very rare:* myocardial infarction. ***Vascular disorders:*** *Uncommon:* flushing, hypertension. *Very rare:* cerebrovascular accident. ***Respiratory, thoracic and mediastinal disorders:*** *Uncommon:* cough, dyspnoea, epistaxis. ***Gastro-intestinal disorders:*** *Common:* gastro-intestinal disorders (e.g. abdominal pain, flatulence, heartburn), diarrhoea, dyspepsia, epigastric discomfort, nausea. *Uncommon:* abdominal distention, acid reflux, bowel movement pattern change, constipation, dry mouth, gastroduodenal ulcer, irritable bowel syndrome, oesophagitis, oral ulcer, vomiting. *Very Rare:* gastro-intestinal perforation and bleeding. ***Skin and subcutaneous tissue disorders:*** *Uncommon:* ecchymosis, facial oedema, pruritus, rash. ***Musculoskeletal, connective tissue and bone disorders:*** *Uncommon:* muscular cramp/spasm, musculoskeletal pain/stiffness. ***Renal and urinary disorders:*** *Uncommon:* proteinuria. ***General disorders and administration site conditions:*** *Common:* asthenia/fatigue, flu-like disease. *Uncommon:* chest pain. ***Investigations:*** *Common:* ALT increased, AST increased. *Uncommon:* blood urea nitrogen increased, creatine phosphokinase increase haematocrit decreased, haemoglobin decreased, hyperkalaemia, leukocytes decreased, platele decreased, serum creatinine increased, uric acid increased. The following serious undesirab effects have been reported in association with the use of NSAIDs and cannot be ruled out f etoricoxib: nephrotoxicity including interstitial nephritis and nephrotic syndrome and ren failure; hepatotoxicity including hepatic failure and jaundice; cutaneo-mucosal adverse effec and severe skin reactions.

PACKAGE QUANTITIES AND BASIC NHS COST

60 and 90 mg Tablets: packs of 28 tablets £22.96; 120 mg Tablets: packs of 7 tablets £5.7

Marketing Authorisation numbers

Tablet 60 mg PL 0025/0422; Tablet 90 mg PL 0025/0423; Tablet 120 mg PL 0025/0424

Marketing Authorisation holder

Merck Sharp & Dohme Limited, Hertford Road, Hoddesdon, Hertfordshire EN11 9BU, U

POM **Date of review:** July 2002

® denotes registered trademark of Merck & Co., Inc., Whitehouse Station, NJ USA.
© Merck Sharp & Dohme Limited 2002. All rights reserved.

MSD
Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon, Hertfordshire EN11 9BU

stones and the oxygen alarm did not sound? If so, please contact:

Dr P. A. Charlebois, 2425 Eglinton Avenue East, Scarborough, Ontario, Canada.

8th International Congress of Cardiothoracic and Vascular Anesthesia
19th International Congress of the Israel Society of Anesthesiologists

Jerusalem, Israel, November 10–13, 2002

For further information regarding the Congress, please contact:
8th International Congress of Cardiothoracic and Vascular Anesthesia, PO Box 50006, Tel Aviv 61500, Israel

Tel: +972 3 5140000; Fax: +972 3 5140077; E-mail: anesth2002@kenes.com

Web address: http://www.isranest.org.il/congress 2002

Primary FRCA Revision Course

Clinical Education Centre, Leicester Royal Infirmary, November 27–29, 2002

An intensive revision course with emphasis on small group tutorial teaching and including MCQ and VIVA practice with individual feedback.

For further information, please contact: Christine Gethins. Tel: 0116 258 5291; E-mail: anae@le.ac.uk

Liverpool Society of Anaesthetists Slim Volume Symposium: Evidence-based anaesthesia and critical care—a slim volume?

Moat House, Chester, UK, November 28–29, 2002

For further details, please contact: Georgina Hall, Department of Anaesthesia, Arrowe Park Hospital, Upton, Wirral, Merseyside CH49 5PE, UK. Tel: +44(0)151 604 7056; Fax: +44(0)151 604 7126; E-mail: georgina.hall@whnt.nhs.uk

Third Euro-PNB Winter Symposium: postgraduate course on peripheral nerve blockade in surgery and pain management for anaesthesiologists

Excelsior Mila Hotel, Crans-Montana, Switzerland, January 16–19, 2003

Meet European experts in this stimulating course and workshops in an exciting environment.

Registration before December 1, 2002 to: Assoc. Professor Alain Borgeat, Department of Anaesthesia and Intensive Care, Orthopedic University Clinic, Balgrist/Zürich, Forchstrasse 340, CH-8008 Zürich, Switzerland. Tel: +41 1 386 38 32; Fax: +41 1 386 16 09; E-mail: agorgeat@balgrist.unizh.ch

21st Annual Symposium: Clinical Update in Anesthesiology and Advances in Techniques of Cardiopulmonary Bypass with International Faculty and Industrial Exhibits

Antigua, West Indies, January 19–25, 2003

For information on abstracts, posters and free papers (deadline: November 4, 2002) please contact: Helen Phillips, Mount Sinai Medical Centre, 1 Gustave L. Levy Place, Box 1010, NY 10029-6574, USA. Tel: +1 212 241 7467; Fax: +1 212 426 2009; E-mail: helen.phillips@mssm.edu

14th SW Thames Anaesthesia Update

Belle Plagne, French Alps, January 27–31, 2003

The scientific programme will include lectures and discussions on: acute and chronic pain; paediatric update; obstetric anaesthesia; neurology and anaesthesia; ITU and relevant medical topics; cardiothoracic anaesthesia; day case surgery; regional blocks; new drugs update; training and education; clinical governance; information technology; free papers, guest speakers, workshops, videos on new drugs, equipment and techniques.

Open to all anaesthetists. Anaesthetists in training presenting papers are eligible for prizes. Deadline for abstracts: December 9, 2002. Meeting approved for CEPD.

For more information and to secure a place please contact: Dr J. B. Liban, Anaesthetic Department, St George's Hospital, Blackshaw Road, London SW17 0QT. Tel: +44 (0) 208725 0018; Fax: +44 (0) 208725 3135; E-mail: liban@mailbox.co.uk; Website: www.doctorsupdates.com (on-line registration).

77th Clinical and Scientific Congress of the International Anesthesia Research Society

New Orleans Marriott, New Orleans, Louisiana, March 22–26, 2003

For further information, please contact:

International Anesthesia Research Society, 2 Summit Park Drive, Suite 140, Cleveland, OH 44131-2553, USA. Tel: +1 216 642 1124; Fax: +1 216 642 1127; E-mail: iarshq@iars.org; Website: www.iars.org

PRESCRIBING INFORMATION

Presentation Transdermal patch with rounded corners. '***Transtec*** 35 µg/h' contains 20 mg of buprenorphine. '***Transtec*** 52.5 µg/h' contains 30 mg of buprenorphine. '***Transtec*** 70 µg/h' contains 40 mg of buprenorphine. **Indications** Moderate to severe cancer pain and severe pain not responding to non-opioid analgesics. ***Transtec*** is not suitable for the treatment of acute pain. **Administration** *Elderly and adults over 18 years:* ***Transtec*** patches should be replaced every 3 days. The dosage is dependent on the severity of the pain and the patient's previous history of analgesic requirements. The usual starting dose for opioid naive patients is 35 µg/h. To transfer patients receiving weak or strong opioids, please refer to the ***Transtec*** SmPC. Analgesia can be increased by increasing patch strength or adding another patch. Do not use more than two patches at a time. *Children under 18 years:* Not recommended. excipient sensitivity, delirium tremens, myasthenia gravis, concurrent administration of monoamine oxidase inhibitors or within 2 weeks of discontinuation of their use, opioid-dependency and narcotic withdrawal treatment. **Precautions and warnings** Increased intracranial pressure, acute alcoholism, convulsive disorders, head injury, shock, reduced consciousness, impaired respiratory function or drugs causing this effect, liver function disorders, febrile patients or other increased skin temperature, history of drug abuse. Patients should not drive or use machines while wearing a patch and for at least 24 hours after the patch has been removed. CNS effects may be intensified when ***Transtec*** patches are applied with other opioids, anaesthetics, hypnotics, sedatives, antidepressants, neuroleptics, alcohol, and drugs that depress respiration. Effects may be intensified with inhibitors of CYP 3A4 and weakened by inducers. **Pregnancy and lactation** Contra-indicated in pregnancy. Avoid dizziness, tiredness, constipation, diaphoresis, dyspnoea, oedema. In common with other strong analgesics: respiratory depression, miosis, rashes, blurred vision, serious allergic reactions, hallucinations, and other psychomimetic effects. **Legal category** CD (Sch3) POM **Package quantities and price *Transtec*** 35 µg/h 5 patches £28.97 ***Transtec*** 52.5 µg/h 5 patches £43.46 ***Transtec*** 70 µg/h 5 patches £57.94 **Marketing authorisation numbers** PL 04539/0014-16 **Marketing authorisation holder** Grunenthal GmbH, Ziegelstrasse 6, 52078 Aachen, Germany Further information is available from Napp Pharmaceuticals Limited, Cambridge Science Park, Milton Road, Cambridge CB4 0GW.

Date of preparation February 2002

® ***Transtec*** and the NAPP device are Registered Trade Marks.

© Napp Pharmaceuticals Limited 2002

A LEADER NAPP IN PAIN CONTROL

The Transtec matrix patch is transforming pain management. Transtec is the first patch licensed for chronic, severe, non-malignant pain. Offering continuous pain relief from a 72-hour patch, Transtec is also associated with a low level of side-effects. So now when you're faced with the challenge of how to manage this type of pain, think square. Think patch. Think Transtec.

new
Transtec®▼
buprenorphine matrix patch

The first patch licensed for malignant pain and chronic, severe non-malignant pain

Advances in Anatomy and Clinical Examination of the Hand and Wrist

Genval (Brussels), Belgium, March 28–29, 2003
Presymposium Hands-on Course of Hand Surgical Anatomy, March 27, 2003

The symposium will promote exchange between scientists and clinicians, and will include presentations by invited faculty. Participants may submit original papers for a limited number of oral presentations, and there will be considerable time reserved for discussion. Deadline for submission of abstracts: December 31, 2002.

For further details, please contact: F. Schuind, MD, PhD, Department of Orthopaedics, Erasme University Hospital, 808 route de Lennik, B-1070 Brussels, Belgium. Tel: +32 2 555 68 44/36 45; Fax: +32 2 520 35 36; E-mail: Hand.congress@ulb.ac.be

German Congress of Anaesthesiology 2003

(DAK 2003)
München, April 9–13, 2003

For further information, please contact:

Medizinisch Congressorganization Nürnberg AG.
Tel: +49 911 393160; Fax: +49 911 331204

International Consensus Conference in Intensive Care Medicine—'Challenges in End-of-Life Care in the ICU'

Brussels, Belgium, April 24–25, 2003

This conference aims to evaluate available scientific knowledge and to advance the understanding of End-of-Life care. The questions to be answered: (i) Is there a problem with End-of-Life care in the ICU?; (ii) What is the 'epidemiology' of death in the ICU?; (iii) Who takes the decision to limit life-sustaining treatments in the ICU?; (iv) What explains the differences between countries and cultures regarding End-of-Life care in the ICU?; (v) What is the optimal care for patients dying in the ICU? Jury will deliberate on April 26–27.

For more information, please contact: ESICM ICC–Mrs Estelle Flament, 40 Avenue Joseph Wybran, B-1070 Brussels, Belgium; Tel: +32 (0)2 559 03 55; Fax: +32 (0)2 527 00 62; E-mail: public@esicm.org; Website: www.esicm.org.

27th Congress of The Scandinavian Society of Anaesthesiology and Intensive Care Medicine

Helsinki, Finland, August 16–20, 2003

A biannually arranged Scandinavian congress in one of the five Scandinavian countries; language: English.

For further information please contact: Prof. Per H. Rosenberg, Helsinki University Hospital, Helsinki FIN00029 HUS, Finland.

E-mail: per.rosenberg@hus.fi
Or: CONGREX/Blue & White Conferences Oy
E-mail: congrex@congrex.fi
Web address: www.congrex.fi

Société Française d'Anesthésie et de Réanimation

Annual congresses will take place in Palais des Congrés, Porte Maillot, Paris on the following dates:

September 18–21, 2003
September 20–October 3, 2004
September 29–October 2, 2005

For further information, please contact: SFAR, 74, rue Raynouard, F-75016 Paris, France. Tel: +33 1 45 25 82 25; Fax: +33 1 40 50 35 22; E-mail SFAR@invivo.edu

Dingle 2003—5th Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 1–5, 2003

For further information contact:

Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Crosspiece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

7th Biennial Congress of the Asian and Oceanic Society of Regional Anesthesia and Pain Medicine

Bangkok, Thailand, November 5–8, 2003

A biennial congress with a scientific programme of special lectures, symposiums, and workshops on various techniques of regional anaesthesia and pain medicine.

For further information, please contact: AOSRA Secretariat, 39 Pradipat 10 (Phaholyothin 11) phyathai, Bangkok 10400, Thailand. Tel: +66 0 2615 7301; Fax: +66 0 2615 7309; Mobile: +66 (01) 836 1368; E-mail: cdm@cdmthailand.com

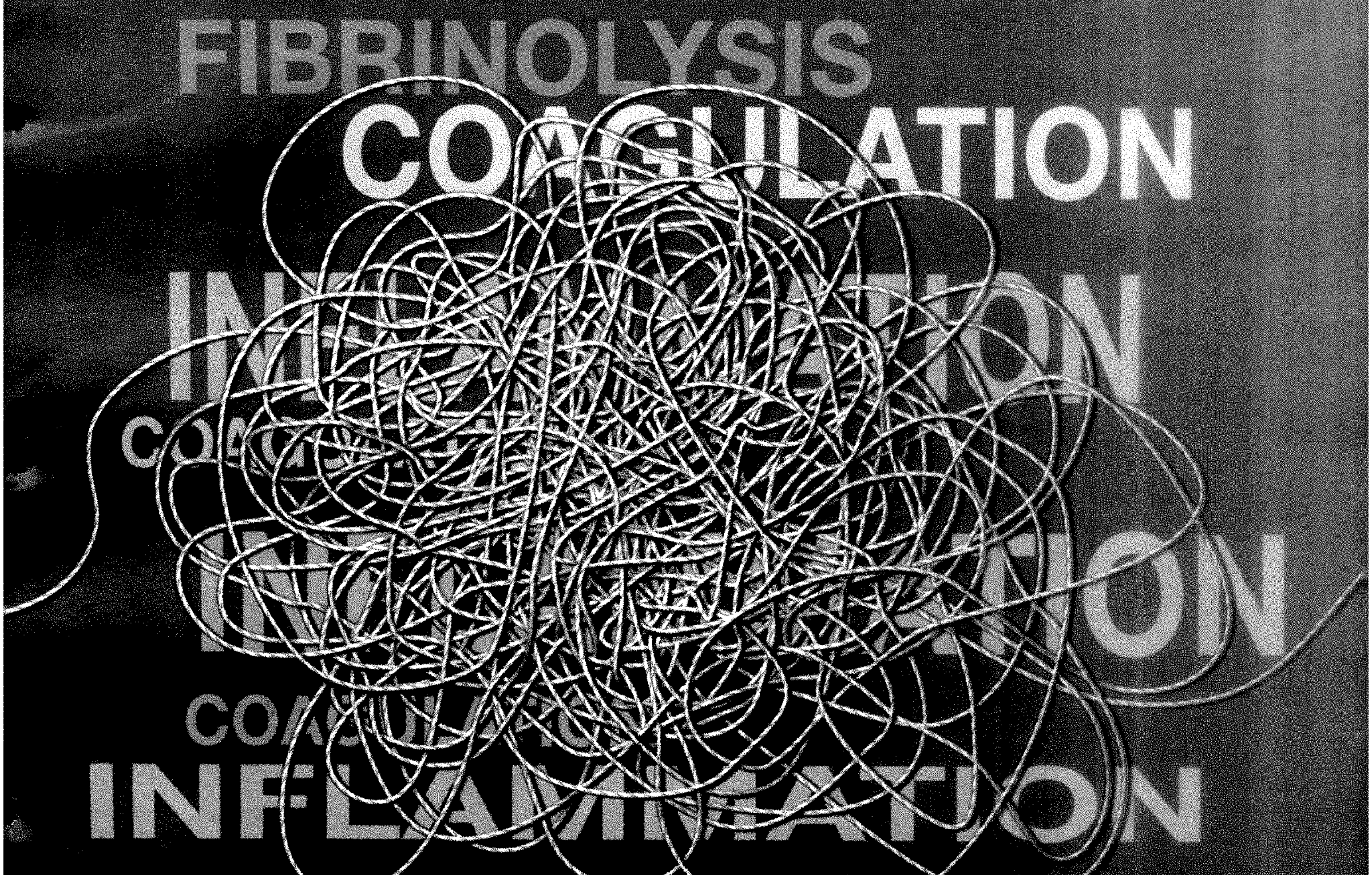
Web address: http://www.cdmthailand.com

13th World Congress of Anaesthesiologists

Palais des Congrès de Paris, Paris, France, April 18–23, 2004

For further details, please contact the Congress Office at: COLLOQUIUM, 12 rue de la Croix Faubin, F-75557

Sepsis is difficult to unravel



Severe sepsis is a complex process. Even with the very best medical efforts, there is still significant mortality. There is now a much better understanding of how inflammation, coagulation and impaired fibrinolysis act together in severe sepsis.

Paris cedex 11, France. Tel: +33 (0) 1 44 64 15 15. Fax: +33 (0) 1 44 64 15 16/17. E-mail: wca2004@colloquium.fr Website: www.wca2004.com

International Anaesthesia Research Society Annual Clinical and Scientific Congresses

78th Clinical and Scientific Congress of the International Anesthesia Research Society, Tampa Marriot Waterside Hotel, Tampa, Florida, March 27–31, 2004

79th Clinical and Scientific Congress of the International Anesthesia Research Society, Hilton Hawaiian Village, Honolulu, Hawaii, March 11–15, 2005

For information please contact: International Anesthesia Research Society, 2 Summit Park Drive, Suite 140, Cleveland, Ohio 44131–2553, USA. Tel: +1 16 642 1124; Fax: +1 216 642 1127; E-mail: iarshq@iars.org; Website: www.iars.org

Introducing

the first injectable COX-2 selective inhibitor

Pain relief with

Starting Power, Staying Power

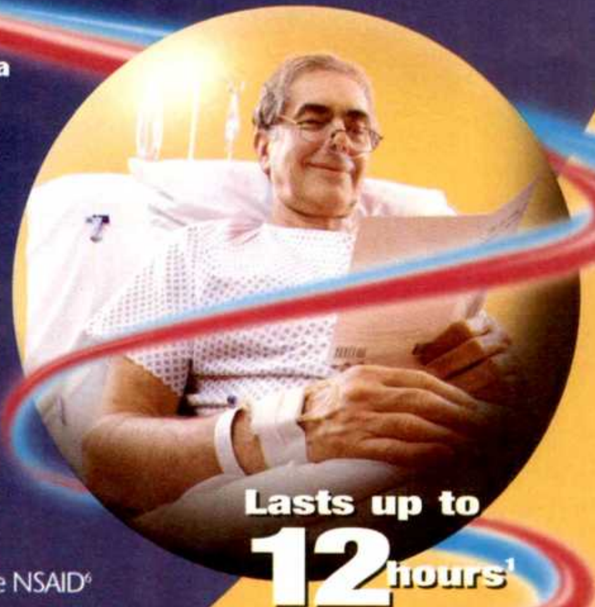
Onset within 7 to 13 minutes[1]

Powerful, effective analgesia
Comparable onset of action and longer lasting efficacy compared to ketorolac 30 mg IV and 60 mg IM[2,3]

Fast acting and long lasting
Proven in a wide range of procedures, including orthopaedic, gynaecological and oral surgery[3,4,5]

No significant increase in bleeding time vs placebo in contrast to a traditional injectable NSAID[6]

Improved upper GI tolerability profile vs an injectable NSAID[7]



Lasts up to 12 hours[1]

New

Dynastat™ ▼ IV/IM

parecoxib sodium

Works fast...and lasts[1]

PHARMACIA

Abbreviated Prescribing Information DYNASTAT Presentation: Vials containing 40 mg parecoxib as powder for solution for injection or vials containing 40 mg parecoxib as powder for solution for injection together with 2 ml ampoules 9 mg/ml (0.9%) sodium chloride. Vials should be reconstituted with 2 ml sodium chloride 9 mg/ml (0.9%) before administration.

Indications: For the short-term treatment of postoperative pain.

Dosage: The recommended dose is 40 mg administered intravenously (IV) or intramuscularly (IM), followed every 6 to 12 hours by 20 mg or 40 mg as required, not to exceed 80 mg/day. *Elderly:* Usual dose may be used. For elderly patients weighing less than 50 kg, initiate treatment with half the usual recommended dose and reduce the maximum daily dose to 40 mg. *Hepatic Impairment:* No dosage adjustment is generally necessary in mild hepatic impairment. In moderate hepatic impairment (Child-Pugh scale 7-9) use with caution and at half the usual recommended dose and reduce the maximum daily dose to 40 mg. Not recommended in severe hepatic impairment (Child-Pugh scale >9). *Renal impairment:* Use caution in renal impairment or patients with fluid retention, however no dosage adjustment is usually necessary. *Children:* Not recommended.

Contraindications: Hypersensitivity to the active substance or to any of the excipients. Patients who have experienced bronchospasm, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria or allergic-type reactions after taking acetylsalicylic acid or NSAIDs or other cyclooxygenase-2 (COX-2) selective inhibitors. In the third trimester of pregnancy and breast-feeding. Severe hepatic impairment (Child-Pugh >9). Active peptic ulceration or gastro-intestinal bleeding. Inflammatory bowel disease. Severe congestive heart failure.

Warnings/Precautions: There is limited clinical experience with Dynastat treatment beyond two days and in certain types of surgery. Caution should be used in coronary artery bypass graft surgery as a higher risk of certain adverse events is observed. Caution in those with dehydration, impaired renal function, hypertension, compromised cardiac or hepatic function (moderate hepatic impairment). Dynastat may mask fever. Monitoring of incisions for signs of infection following surgery is advised. Caution in those with history of PUBs. Dynastat is not a substitute for acetylsalicylic acid (aspirin) in CV prophylaxis. Caution when used concomitantly with warfarin. Not recommended in women attempting to conceive.

Interactions: *Pharmacodynamic:* Monitor anticoagulant therapy due to increased risk of bleeding complications, however Dynastat does not affect pharmacodynamics of heparin. No effects observed on acetylsalicylic acid-mediated platelet aggregation. As for NSAIDs, may reduce the effect of diuretics, antihypertensives or increase risk of acute renal insufficiency. Monitor renal function when co-administered with NSAIDs, tacrolimus or cyclosporin. May be co-administered with opioid analgesics with a consequential reduction in the dose of morphine to achieve same level of analgesia. *Pharmacokinetics:* The dose of parecoxib sodium should be reduced when co-administered with fluconazole, a CYP2C9 inhibitor. No dosage adjustment is required when administered with ketaconazole (CYP3A4). Metabolism of the active moiety, valdecoxib may increase with enzyme inducers such as rifampicin, phenytoin, carbamazepine or dexamethasone. Caution should be observed with co-administration of medicines metabolised by CYP2D6 (eg. flecainide, propafenone, metoprolol), or substrates of CYP2C19 (eg. phenytoin, diazepam, imipramine). Monitor for methotrexate-related toxicity when given together. Lithium serum concentrations should also be monitored when given concomitantly as lithium clearance may be reduced. No kinetic or clinically significant effects have been observed when given together with injectable anaesthetics eg propofol or midazolam or inhalation anaesthetic agents nitrous oxide and isoflurane.

Adverse Effects: *Common (≥1/100, <1/10)* hypertension, hypotension, back pain, peripheral oedema, hypoaesthesia, alveolar osteitis (dry socket), dyspepsia, flatulence, creatinine increase, hypokalaemia, agitation, insomnia, postoperative anaemia, pharyngitis, respiratory insufficiency, pruritus, oliguria. *Uncommon (≥1/1000, <1/100)* aggravated hypertension, abnormal sternal serous wound drainage, wound infection, gastroduodenal ulceration, bradycardia, SGOT/SGPT increased, BUN increased, ecchymosis, thrombocytopenia, cerebrovascular disorder. The following rare, serious adverse events have been reported in association with the use of NSAIDs and cannot be ruled out for Dynastat: acute renal failure, congestive heart failure, anaphylactic shock, bronchospasm, hepatitis. Following coronary artery bypass graft surgery, patients administered Dynastat may have a higher risk of adverse events, such as cerebrovascular accident, renal dysfunction or sternal wound complication.

Packaging Quantity and Price:

Strength	Pack size	NHS price
40 mg (no diluent)	10	£49.60
40 mg (with diluent)	5	£28.34

Marketing Authorisation Numbers and Holder: EU/1/02/209/005 (10's) EU/1/02/209/008 (5+5's), Pharmacia Europe EEIG, Hillbottom Road, High Wycombe, HP12 4PX, UK.
Legal Category: POM.
Date of Preparation: April 2002.

References: 1. DYNASTAT SmPC 2002. **2.** Data on file. DYNASTAT Integrated Summary of Efficacy. 2000. Pharmacia Corporation, Peapack, NJ. **3.** Daniels SE, Grossman EH, Kuss ME *et al.* Clin Ther 2001;**23**(7):1018-1031. **4.** Langeland FF, Turpin M, Waller P *et al.* 2000 American Pain Society Abstract Database, Poster No. 814. **5.** Hubbard RC, Stulberg BN, Yorn S. ASA Meeting Abstracts. Abstract A-807. **6.** Data on file. DYNASTAT Integrated Summary of Safety Information. 2000. Pharmacia Corporation, Peapack NJ. **7.** Stolz RR Harris SI, Kuss ME et al. Am J Gastroenterol 2002;**97**(1):65-71

P7592/3/02

Breathing Systems

for anaesthesia

Features

- A wide range of Breathing Systems for all applications
- Available in Flextube™, Smoothbore and Compact tubing
- Adult, Paediatric and Neonatal versions available

For a quality service with a personal touch contact your local office or alternatively visit www.intersurgical.com

INTERSURGICAL®
COMPLETE RESPIRATORY SYSTEMS

Deutschland
T 02241 311063
info@intersurgical.d

France
T 01 48 76 72 30
info@intersurgical.f

España
T 91 665 73 15
info@intersurgical-es.c

Portugal
T 21 910 85 50
info@intersurgical.p

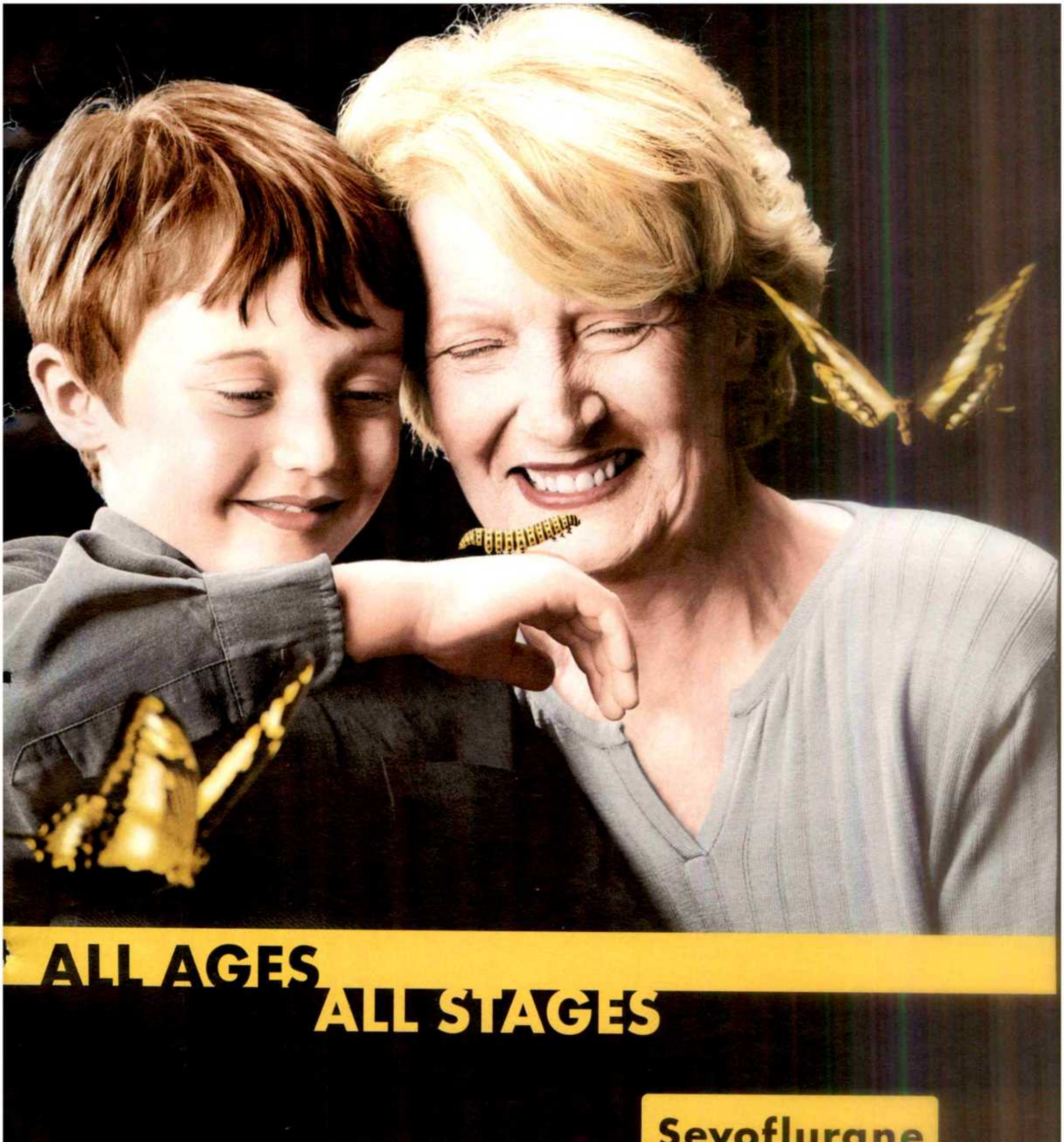
Lietuva
T 370387 66611
info@intersurgical.

Nederland
T 0413 243860
info@intersurgical.

Россия
T 095 935 8659
info@intersurgical.

United Kingd
Crane House
Molly Millars La
Wokingham
RG41 2RZ

T + 44 (0)118 9656
F + 44 (0)118 9656
info@intersurgical.c



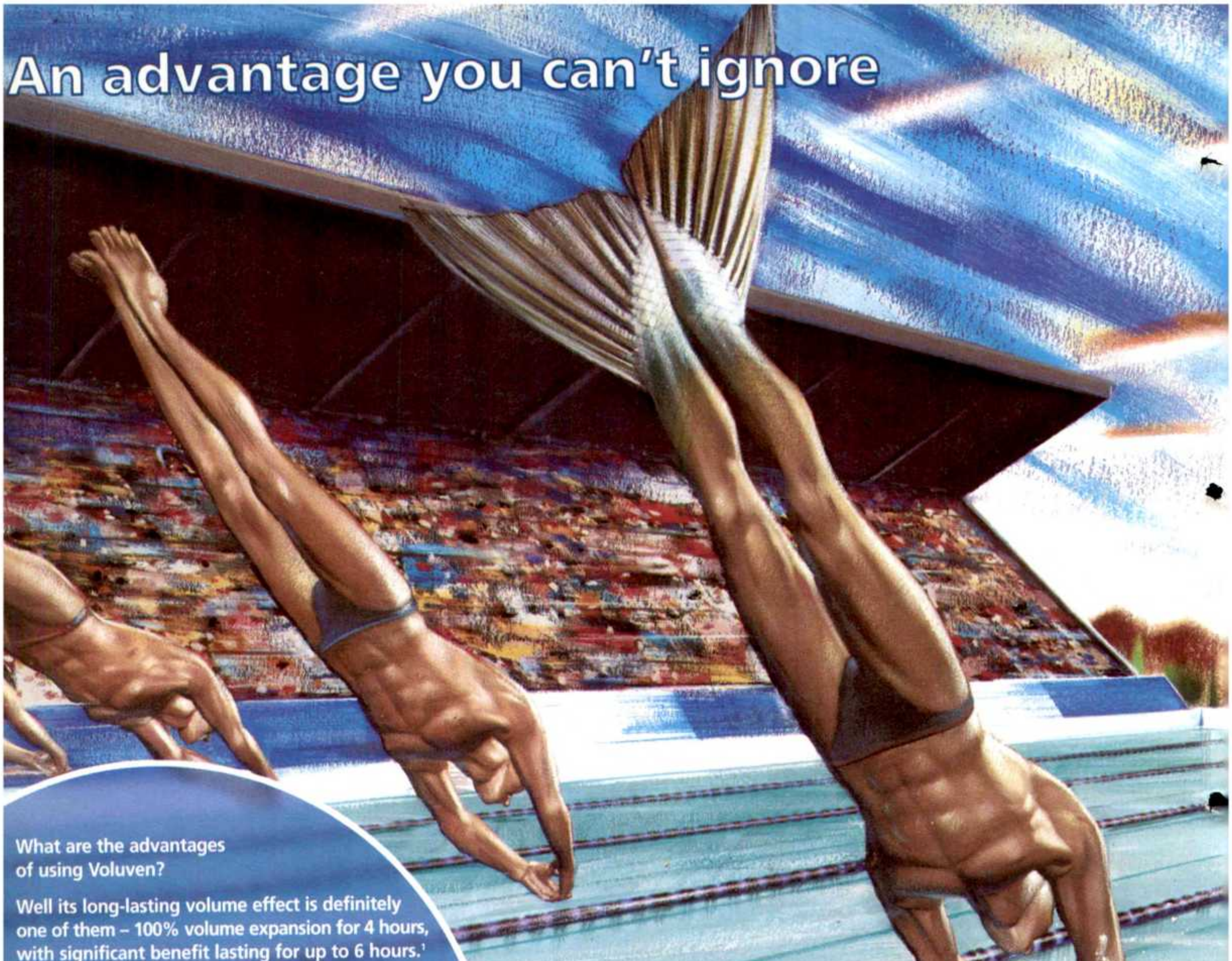
Sevoflurane

FROM INDUCTION TO MAINTENANCE

oflurane Prescribing Information. Presentation: Amber bottle containing 250ml sevoflurane. **Indications:** For induction and tenance of general anaesthesia in adult and paediatric patients for inpatient and outpatient surgery. **Dose:** MAC values decrease with and the addition of nitrous oxide (see Summary of Product Characteristics). *Induction:* In adults up to 5% sevoflurane usually produces cal anaesthesia in less than 2 minutes; in children up to 7% sevoflurane usually produces surgical anaesthesia in less than 2 minutes. Up % sevoflurane can be used for induction in unpremedicated patients. Maintenance concentrations range from 0.5–3%. *Elderly:* lesser ntrations normally required. **Administration:** Deliver via a vaporiser specifically calibrated for use with sevoflurane. Induction can be ved and maintenance sustained in oxygen or oxygen-nitrous oxide mixtures. **Contra-indications:** Sensitivity to sevoflurane. Known or cted genetic susceptibility to malignant hyperthermia. **Precautions:** For use only by trained anaesthetists. Hypotension and respiratory ssion increase as anaesthesia is deepened. Malignant hyperthermia. Experience with repeat exposure is very limited. Until further data btained, sevoflurane should be used with caution in patients with renal insufficiency. Levels of Compound A (produced by direct contact CO_2 absorbents) increase with: increase in canister temperature; increase in anaesthetic concentration; decrease in gas flow rate and se more with the use of Baralyme rather than soda lime. **Interactions:** Potentiation of non-depolarising muscle relaxants. Similar to use of an IV anaesthetic. Sevoflurane metabolism may be induced by CYP2E1 inducers, but not by barbiturates. **Side-Effects:** Dose-dependent cardio-respiratory depression. The type, severity and frequency of adverse events are comparable to those seen with other inhalation anaesthetics. Most adverse events are mild to moderate and transient: nausea, vomiting, increased cough, hypotension, agitation and bradycardia. Hepatitis has been reported rarely. Convulsions may occur extremely rarely, particularly in children. There have been very rare reports of pulmonary oedema. As with other anaesthetics, twitching and jerking movements, with spontaneous resolution have been reported in children during induction. Patients should not be allowed to drive for a suitable period after sevoflurane anaesthesia. **Use in Pregnancy and Lactation:** Use during pregnancy only if clearly needed. It is not known whether sevoflurane is excreted in human milk – caution in nursing women. **Overdose:** Stop sevoflurane administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen and maintain adequate cardiovascular function. **Special Storage Conditions:** Do not store above 25°C. Do not refrigerate. Keep cap tightly closed. **Legal Category:** POM **Marketing Authorisation Number:** PL 0037/0258. **Basic NHS Price:** 250ml bottle £123.00. Further information is available on request from Abbott Laboratories Ltd., Abbott House, Norden Road, Maidenhead, Berkshire SL6 4XE. **Ref.** PI/12/009

ABBOTT ANAESTHETICS

An advantage you can't ignore



What are the advantages of using Voluven?

Well its long-lasting volume effect is definitely one of them – 100% volume expansion for 4 hours, with significant benefit lasting for up to 6 hours.[1]

And then there's its safety profile.

It has been specifically designed to reduce the risk of side effects, particularly effects on clotting, that have been associated with gelatins and high molecular weight starches.[2,3]

And its renal elimination profile is higher than that of other HES specifications, so consequently tissue storage is reduced.[4]

So, if the situation demands a colloid – demand Voluven.

VOLUVEN®

6% hydroxyethyl starch 130/0.4

Giving you an edge over other colloids

Voluven Prescribing Information

Voluven® 6% Solution for Infusion.

Active substance: 1000ml contains 60g hydroxyethyl starch (mean molecular weight: 130,000; molar substitution 0.38-0.45). **Indications:** Therapy and prophylaxis of hypovolaemia. **Dosage and administration:** For continuous IV infusion. Daily dose and rate of infusion depend on patient blood loss and haemodynamic parameters. The maximum daily dose is 50ml/kg/day. **Contra-indications:** Fluid overload, renal failure with oliguria or anuria, patients receiving dialysis treatment, intracranial bleeding, severe hypernatraemia or severe hyperchloraemia, known hypersensitivity to hydroxyethyl starches. **Precautions:** Avoid fluid overload. In cases of severe dehydration a crystalloid solution should first be given. Care must be taken in patients with severe liver disease or severe bleeding disorders. There are no data available on the use of Voluven® in children. It is important to supply sufficient fluid and to regularly monitor kidney function and fluid balance. **Undesirable effects:** Hydroxyethyl starch may cause anaphylactoid reactions in very rare cases. The concentration of serum amylase can rise during administration of hydroxyethyl starch and can interfere with the diagnosis of pancreatitis. Pruritus (itching) after prolonged administration of high dosages is a known undesirable effect of hydroxyethyl starches. At high dosages the dilution effects may result in a corresponding dilution of blood components such as coagulation factors and other plasma proteins and in a decrease of haematocrit. With the administration of hydroxyethyl starches disturbances of blood coagulation can occur depending on the dosage. **Marketing authorisation holder:** Fresenius Kabi Ltd, Melbury Park, Birchwood, Warrington, WA3 6FF. **MA numbers:** UK – PL 08828/0145, IRE – PA 566/20/1. **Legal category:** POM. **Cost:** UK £12.50 per 500ml, Ireland €15.24 per 500ml. **Date of revision:** May 2002.

References

1. Waitzinger J, *et al*. Effect of a new HES specification (6% HES 130/0.4) on blood and plasma volumes after bleeding in 12 healthy male volunteers. Clin Drug Invest 1999; **17:** 119-125.
2. Ragaller MJR, *et al*. Volume replacement in critically ill patients with acute renal failure. J Am Soc Nephrol 2001; **12:** S33-S39.
3. Baron J-F. A new hydroxyethyl starch: HES 130/0.4, Voluven®. Transf Alt Transf Med 2000; **2:** 250.
4. Waitzinger J, *et al*. Pharmacokinetics and tolerability of a new hydroxyethyl starch (HES) specification [HES (130/0.4)] after a single dose infusion of 6% or 10% solution in healthy volunteers. Clin Drug Invest 1998; **16:** 151-160.

Fresenius
Kabi

BJA

"I would have everie man write what he knowes and no more."—Montaigne

BRITISH JOURNAL OF ANAESTHESIA

Volume 89, Number 5, November 2002

Editorial I

Live and let die? A structured approach to decision-making about resuscitation

Clinical decision-making is under attack. Such reports as 'Cancer patient's fury at doctor who "wrote her off" on hospital's death ward',[1] and hospital found guilty,[2] as 'keeping Miss B alive was an unlawful act', mean we could be forgiven for being confused (and defensive). We have taken off our white coats and first name terms are fashionable, yet the public and the profession are restive.

In the first case referred to above,[1] a patient in her late sixties receiving chemotherapy for gastric cancer, was admitted to hospital with septicaemia. After treatment, she was 'horrified' to discover that 'inappropriate for resuscitation' had been written in her notes. 'They were going to let me die,' she is reported to have said. All the emotive elements were there—secrecy, paternalism, doctors yet again acting as gods, denial of choice, in an age when consumerism has itself become a god, and death itself—the real enemy. Age Concern saw it as an example of ageism in the NHS.[3] At the heart of the ensuing uproar was the view that patients should have the right to decide whether or not there should be medical intervention.

In a swift political response,[4] Hospital Trusts were directed to implement resuscitation policies based on the recently revised BMA/Resuscitation Council (UK)/RCN document.[5]

BMA/Resuscitation Council (UK)/RCN document (the Resuscitation document)

The aim of this document was to outline legal and ethical standards for planning patient care and making decisions in relation to cardiopulmonary resuscitation (CPR). It succeeded in addressing an emotive issue, but in trying to find common ground, compromised some ethical and legal principles, which prompted the Association of Palliative Medicine (APM) and the National Hospice Council (NHC) to issue a joint statement.[6]

The points causing the APM and NHC concern were:

1. The fall back position of the Resuscitation document is to attempt resuscitation, that is 'there should be a presumption that health professionals will make all reasonable efforts to attempt to revive the patient'.
2. In making an advance decision that CPR will not be attempted (a do not attempt resuscitation order—DNAR), the Resuscitation document states 'where competent patients are at foreseeable risk of cardiopulmonary arrest, or have a terminal illness, *there should be sensitive exploration of their wishes regarding resuscitation.* This will *normally* arise as part of general discussions about the patient's care'.
3. The Resuscitation document suggests conflicting duties for doctors.[7] 'Doctors cannot be required to give treatment contrary to their clinical judgement, but should respect, whenever possible, patient's wishes to receive treatment which carries only a very small chance of success or benefit.'

Let us consider these three concerns, with respect to clinical evidence, ethics and the law.

Resuscitation: clinical evidence

The indications for CPR, as for any medical intervention, depend on its effectiveness. This has been broadly classified by Warlow,[8] as treatments which either:

(a) definitely improve outcome,
(b) do not improve outcome at all and should be abandoned,
(c) are simply dangerous and should be banned, or
(d) we are not sure about, but are promising and should be subject to further research.

When introduced 40 yr ago, CPR was intended to prevent premature death in previously 'fit' patients, who sustained a sudden cardiac or respiratory arrest. It was never intended to be part of every death,[9] and yet it is now attempted in many irreversible situations, in which not surprisingly, it has shown little if any benefit.

The public and some health professionals, have an unrealistic perception of the benefit of CPR,[10] and the idea that DNAR equates with abandonment of good medical care. A review of cardiac arrests in the most popular American television medical programmes[11] (ER, Chicago Hope, and Rescue 911) found that outcome tended to be simplified to life or death, ignoring the real risk of disability or persisting unconsciousness. The majority of cases were young (children, teenagers, or young adults) and the majority of cardiac arrests were because of trauma (shoot-

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

ings, road accidents, drowning). Only 12% had underlying illness. In this fictional world, 75% of patients survived the arrest and 67% were subsequently well enough to go home. In a subtle way, as Diem says,[11] 'the misrepresentation of CPR on television undermines trust in data and fosters trust in miracles'.

In real life, the denominator is different. The average hospital patient is likely to be older, sicker, and with significant underlying disease. A more realistic UK figure,[12] is a short-term success rate (defined as restoring arterial pressure for 1 h), in two out of five resuscitation attempts, and a one in eight long-term success rate (defined as well enough to be discharged). Survival is much worse for those who have underlying non-cardiac illness and/or poor performance status before the arrest.[13] In patients with advanced malignancy, it is dismal.[14]

It is not the presence of cancer *per se* which is the issue, but performance status and extent of the disease. In a recent review of 243 cancer patients, who arrested in hospital,[14] the most significant independent prognostic factor of survival was the nature of the arrest. Of those who arrested suddenly and unexpectedly, 22% (16/73) left hospital. Of those whose deterioration beforehand was gradual and unrelenting, none (0/171) survived ($P<0.001$).

Thus, CPR may be lifesaving in patients with a previously good performance status who have a sudden, unexpected event (Warlow group a). It will almost certainly not work and should be abandoned in patients with advanced cancer and those with extensive and irreversible underlying disease whose general condition is deteriorating (Warlow groups b and c). Finally, it may achieve an agreed benefit for other groups, which needs to be identified through further research (Warlow group d).

Thus, referring to concern number 1 of the Resuscitation document, the APM/NHC considers a presumption in favour of CPR is inappropriate for large groups of hospital in-patients. Secondly, the patients with whom discussion about CPR is to be encouraged (concern number 2), that is those who are at foreseeable risk of cardiac arrest or who have a terminal illness, are the group who are unlikely to benefit. The APM/NHC statement therefore, reaffirms there is no obligation to discuss CPR with those patients for whom treatment is judged to be futile.

Decision-making: ethics

Four ethical principles summarize our moral responsibility to others: beneficence (do good), non-maleficence (avoid harm), justice (effective medical interventions should be universally available), and autonomy (respect for individual deliberated choice and confidentiality).

Applying these to CPR, we have a moral responsibility to do good to others (beneficence); and to guard the patient and society against the unscrupulous application of medical technology of no proven benefit. CPR should, therefore, be carried out only when likely to be effective. Secondly, we have a moral responsibility to avoid harming others (non-maleficence). CPR should not be performed when it is neither clinically indicated, nor wished by the patient. A physician is required only to provide medical benefit to patients—no ethical principle has ever required doctors to do what is of no net benefit and is in the extreme, physiologically futile. In other words, withholding an ineffective intervention is ethically sound. Furthermore, providing it is degrading, unpleasant, and undignified. With reference to concern number 3 from the Resuscitation document, the APM/NHC reaffirms that no doctor can be required to deliver a treatment, which is not clinically justifiable.

Justice demands that effective medical intervention should be universally available. Hence, ineffective CPR fails justice criteria. And finally there is autonomy. A patient who might benefit from CPR, has the right to state in advance they do not wish it, even if it were medically appropriate. This does not imply a right to demand CPR, but the notion of autonomy has become so powerful that 'its glare often blinds physicians'.[15] Judgement demands we balance all ethical principles.

Decision-making: the law (UK)

Issues relevant to CPR are the concepts of best interest and capacity. Two new pieces of legislation are relevant: the Human Rights Act, 1998,[16] and Adults with Incapacity (Scotland) Act, 2000.[17]

Although some cynics may choose to believe that best interest 'is a phrase doctors use to justify pursuing their own',[18] the law clearly states that doctors have a legal duty to apply good medical practice in the best interests of their patient. No law has ever required doctors to do what is, on best evidence, extremely unlikely to achieve the intended aim. Indeed, where treatment is not necessary and not in the best interest of the patient, there is no authority for providing treatment (concern number 3), and in fact to do so could be considered assault. Applying the best interests test, as in the cases of Johnstone (Scotland),[19] and Bland (England),[20] it can be argued that it is not that the best interest may be served by the patient being allowed to die, but that it would be in their best interest *not* to be subjected to a medically futile CPR attempt. Article 3 of the Human Rights Act aims to protect patients from inhuman, degrading, or experimental treatment, and it could be argued that treatment which is not properly established, may be considered experimental.[16]

With regard to capacity, patients who have a cardiac arrest obviously do not have the capacity to consent or otherwise to treatment. The law is clear that the doctor is responsible for deciding, on the basis of the best interests test, what action to take. This considers medical evidence, and where relevant, the patient's known views and/or the understanding that relatives may have, of what the patient may have wished.

Decision-making: the evidence

There is increasing evidence that patients wish to be more involved than their doctors think,[21 22] and the GMC has set clear standards for doctors respecting the rights of patients to be fully involved in decisions about their care. However, not all patients feel comfortable being actively involved in decision-making.[23] Furthermore, making decisions when well is different from making decisions when ill, frail or frightened, when it may be an intolerable burden.

Patients cannot choose to be involved, if they are not given enough relevant information. Certainly in cancer patients, there is overwhelming evidence that patients and their relatives want more information—90% say they want as much as possible, good, or bad.[21] Yet it has not proved possible to answer the simple question 'Does giving more information improve decision-making?'[22] This is in part a result of the lack of randomized controlled trials, but perhaps there can be no simple answer, as it would imply some decisions are better than others.

Not everyone wants extensive information, at all stages of their illness, and the reasons for this are complex and human.[23] It takes time to piece together the story of an illness in an understandable way, and patients may choose not to discuss it with us, or they may choose to discuss it today but not tomorrow. Meaningful discussion cannot take place if patients are in pain or symptomatic, and there is much evidence that symptom control is frequently poor in patients with advanced cancer.[24]

Does the threat of immediate death override all medical, moral, ethical, and legal considerations? In these increasingly fearful times, offering an almost certain futile attempt at CPR might seem preferable to risking litigation from a family who may wish it. However, decision-making for CPR is no different from that of any other medical decision, including the need for invasive investigations or unpleasant treatments.

CPR in advanced illness

Discussing CPR soon after admission (concern number 2) may be dangerous for us all. It distracts us from what is important, that is the diagnosis, the extent of the illness, and what we, and the patient, understand by their illness (prognosis). If we persevere with treatment, as if each intervention will be the answer, we will reach a stage when it becomes obvious that nothing else can be done for the patient. By this time, the patient may be too ill to discuss their care. Patients are often unaware how advanced their illness is, through denial (their choice), or lack of discussion (our choice), or because things are unravelling quickly. Some may never accept how ill they are, but in order to help patients to readjust to what is happening, they must be given the opportunity to discuss their situation earlier. We need to recognize the shift from curative to palliative management and in a recent systematic review of patients with advanced cancer,[25] clinical judgement was only one of several independent predictors, which identified patients at risk of dying within 3 months. The time to learn that dying is a possibility, is not when one is burdened with a decision to sign up for CPR or otherwise.

Summary

The law and ethics as they stand provide a framework by which decisions about withdrawing or withholding treatment may be made.[26] If there is nothing to suggest that an intervention is in the patient's best interests, it is ethically and legally appropriate not to provide it. Already we are seeing some cruel, unintended consequences of CPR policies.[27] The debate needs to be broadened,[28] or the belief that death is accidental and not inevitable will prevail. There will always be some uncertainty and it would be more useful to ask doctors and patients what their understanding is, at each stage of the illness.

And there is always another side to the story. Perhaps patients are worried about the same issues as we are—that it is increasingly difficult to care in a more fragmented impersonal system. Faced with increasingly complex medical problems, we should not yield to policy, which we judge to be maleficent—it will make things worse.

P. Levack
Roxburghe House
Jedburgh Road
Dundee DD2 1SP
UK

References

1 Cancer patient's fury at doctor who 'wrote her off on hospital's death ward'. *The Guardian*, April 13, 2000
2 Keeping Miss B alive was an unlawful act *The Times*, March 23, 2002
3 *The Beginning of the End to the Scandal of 'Not for Resuscitation'*. Age Concern England. Astral House, 1268 London Road, London; 2001
4 NHS Executive Resuscitation policy (HSC 2000/028) September, 2000 (England). Scottish Executive Health Department Resuscitation policy (HDL 2000/22), Edinburgh Scottish Executive; November, 2000
5 British Medical Association, Resuscitation Council (UK), Royal College of Nursing. Decisions relating to cardiopulmonary resuscitation: a joint statement from the British Medical Association, the Resuscitation Council (UK) and the Royal College of Nursing. *J Med Ethics* 2001; **27**: 310–6
6 Joint Working Party between the National Council for Hospice and Specialist Palliative Care Services and the Ethics Committee of the Association for Palliative Medicine of Great Britain and Ireland. *Ethical Decision Making in Palliative Care. Cardiopulmonary Resuscitation (CPR) for People who are Terminally Ill.* National Council for Hospice and Specialist Palliative Care Services, 34–44 Britannia St., London, UK, August, 2001

7 Randall F. Recent guidance on resuscitation: patients' choices and doctors' duties. *Palliat Med* 2001; **15**: 449–50

8 Warlow C. The scientific basis of clinical effectiveness: setting the scene. *Proc R Coll Physicians Edinb* 2001; **31**: 9–12

9 Tunstall-Pedoe H. Do not resuscitate decisions. Resuscitation should not be part of every death. *Br Med J* 2001; **322**: 102–3

10 Thorns AR, Ellershaw JE. A survey of nursing and medical staff views on the use of cardiopulmonary resuscitation in the hospice. *Palliat Med* 1999; **13**: 449–50

11 Diem SJ, Lantos JD, Tulsky JA. Cardiopulmonary resuscitation on television. Miracles and misinformation. *N Engl J Med* 1996; **334**: 1578–82

12 Tunstall-Pedoe H, Bailey L, Chamberlain DA, Marsden AK, Ward ME, Zideman DA. Survey of 3765 cardiopulmonary resuscitations in British hospitals (the BRESUS study): methods and overall results. *Br Med J* 1992; **304**: 1347–51

13 Hilberman M, Kutner J, Parsons D, Murphy D. Marginally effective medical care: ethical analysis of issues in cardiopulmonary resuscitation (CPR). *J Med Ethics* 1997; **23**: 361–7

14 Ewer MS, Kish SK, Martin CG, Price KJ, Feeley TW. Characteristics of cardiac arrest in cancer patients as a predictor of survival after cardiopulmonary resuscitation. *Cancer* 2001; **92**: 1905–12

15 Schneiderman LJ, Jecker NS, Jonsen AR. Medical futility: its meaning and ethical implications. *Ann Intern Med* 1990; **112**: 949–54

16 Human Rights Act, 1998. The Stationery Office; October, 2000

17 Adults with Incapacity (Scotland) Act, 2000 Edinburgh: The Stationery Office; 2000

18 O'Donnell M. *A Sceptic's Medical Dictionary*. London: BMJ Publishing, 1997: 145

19 Law Hospital NHS Trust vs Lord Advocate S.C. 301; 1996

20 Airedale NHS Trust vs Bland I *All E.R.* 821; 1993

21 Jenkins V, Fallowfield L, Saul J. Information needs of patients with cancer. Results from a large study in UK cancer centres. *Br J Cancer* 2001; **84**: 48–51

22 Sowden AJ, Forbes C, Entwistle V, Watt L. Informing, communicating and sharing decisions with people who have cancer. *Qual Health Care* 2001; **10**: 193–6

23 Leydon GM, Boulton M, Moynihan C, *et al.* Cancer patients' information needs and information seeking behaviour: in depth interview study. *Br Med J* 2000; **320**: 909–13

24 Twycross R, Harcourt J, Bergl S. A survey of pain in patients with advanced cancer. *J Pain Symp Manage* 1996; **12**: 273–82

25 Vigano A, Dorgan M, Buckingham J, Bruera E, Suarez-Almazor ME. Survival prediction in terminal cancer patients: a systematic review of the medical literature. *Palliat Med* 2000; **14**. 363–74

26 British Medical Association. *Withholding and Withdrawing Life Prolonging Medical Treatment.* 2nd Edn. London: BMJ Books, 2001; 65–70

27 Levack P, Cairns I, Dryden H, Guild P. Doctors' management should not make things worse for patients. *Br Med J* 2002; **324**: 172–3

28 Saunders J. Perspectives on CPR: resuscitation or resurrection? *Clin Med* 2001; **1**: 457–60

British Journal of Anaesthesia 89 (5): 687–92 (2002)

BJA

CLINICAL INVESTIGATIONS

Cerebral haemodynamics in pregnancy and pre-eclampsia as assessed by transcranial Doppler ultrasonography

R. W. Sherman, R. A. Bowie, M. M. E. Henfrey, R. P. Mahajan* and D. Bogod

University Department of Anaesthesia, Nottingham City Hospital, Nottingham NG5 1PB, UK
**Corresponding author: University Department of Anaesthesia and Critical Care, Queen's Medical Centre, Nottingham NG7 2UH, UK*

Background. Altered cerebral circulation, as reported during normal pregnancy, and in patients with pre-eclampsia, can be associated with changes in cerebral vascular reactivity and/or cerebral autoregulation. The aim of our study was to perform a comparative assessment of cerebral haemodynamics, including vascular reactivity and autoregulation, in pre-eclamptic patients, healthy pregnant women, and healthy non-pregnant women.

Methods. Thirty patients with pre-eclampsia were recruited. Age- and height-matched healthy pregnant (n=30) and non-pregnant control (n=30) groups were also recruited. Monitoring included transcranial Doppler ultrasonography, end-tidal carbon dioxide and non-invasive arterial pressure measurement. Cerebral autoregulation was assessed by performing the transient hyperaemic response (THR) test. The cerebrovascular reactivity to carbon dioxide ($CRCO_2$) was assessed by measuring middle cerebral artery blood flow velocity (MCAFV) after induced changes in end-tidal carbon dioxide. Estimated cerebral perfusion pressure (eCPP) and critical closing pressure (CrCP) were calculated using established formulae. Statistical analysis included ANOVA with Tukey's pairwise comparisons.

Results. Mean arterial pressure (MAP) was increased in pre-eclampsia ($P<0.05$). Mean MCAFV was lower in healthy pregnancy ($P<0.05$), but in pre-eclampsia it was similar to the non-pregnant group. When compared with the non-pregnant group, mean eCPP was higher in the healthy pregnant and pre-eclamptic groups ($P<0.05$). There were no meaningful differences in cerebral autoregulation or $CRCO_2$.

Conclusions. Healthy pregnancy increases eCPP, presumably by decreasing CrCP. In pre-eclampsia, eCPP is maintained at the same level as in healthy pregnancy despite an increased MAP. Pre-eclampsia has no significant effect on cerebral autoregulation or $CRCO_2$.

Br J Anaesth 2002; **89**: 687–92

Keywords: complications, pre-eclampsia; measurement techniques, Doppler ultrasound; brain, blood flow; cardiovascular system, effects

Accepted for publication: June 24, 2002

Pregnancy induces widespread changes in the cardiovascular system.[1 2] Cerebral blood flow has been shown to be increased by up to 25% in the first trimester,[3] but it reduces with increasing gestational age and, in the third trimester, it remains at up to 15% more than that in the non-pregnant state.[4 5] Pre-eclampsia has been shown to be associated with an increased middle cerebral artery blood flow velocity (MCAFV) and abnormal transcranial Doppler (TCD) findings compared with the healthy pregnant state.[6] This increase in MCAFV is thought to be secondary to vasospasm and cerebral oedema.[6 7] During induction of anaesthesia, increases in MCAFV associated with increases in arterial pressure in pre-eclamptic patients have been reported to be significantly more than the increases seen in patients with a healthy pregnancy.[8] Changes in vascular tone can affect cerebral perfusion pressure (CPP) by altering the critical closing pressure (CrCP) of cerebral arterioles.[7] Despite reported changes in cerebral blood flow during

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

pregnancy and pre-eclampsia, [3–5] the effects of pregnancy with or without pre-eclampsia on cerebral vascular reactivity, cerebral autoregulation, CPP, and CrCP have not been well documented.

Non-invasive assessment of cerebral haemodynamics using TCD ultrasonography has recently gained importance. Essentially, TCD measures flow velocity in the insonated vessel and the changes in flow velocity can be taken to reflect the changes in blood flow, assuming that the diameter of the insonated vessel remains constant. As TCD is easy to use and gives reproducible measurements, it has become a widely accepted method of assessing the cerebrovascular reactivity to carbon dioxide ($CRCO_2$), cerebral autoregulation, estimated (e)CPP, and CrCP.[7 9–15] In patients with neurological disorders, impairment in both cerebral autoregulation and cerebral vascular reactivity has been shown to predict poor neurological outcome.[15–17] Knowledge of the effects of normal pregnancy and pre-eclampsia on cerebral haemodynamics is essential for appropriate management of these patients undergoing anaesthesia or in labour, particularly when vasoactive medications are administered.

The aim of the present study was to make a comparative assessment of cerebral haemodynamic variables such as cerebral autoregulation, $CRCO_2$, eCPP, and CrCP, using TCD in pre-eclamptic patients, healthy pregnant women, and healthy non-pregnant women.

Materials and methods

After obtaining hospital ethics committee approval and written informed consent, we recruited 30 pre-eclamptic women, in the third trimester of pregnancy, from the obstetric unit. Pre-eclampsia was defined as an arterial pressure greater than 140/90 mm Hg on two separate occasions, with associated proteinuria (>2+ on dipstick and/or >0.3 g $litre^{-1}$ on a 24-h collection), occurring after the 20th week of gestation. Healthy pregnant (third trimester; n=30) and non-pregnant women, matched for age and height to the pre-eclamptic women, were also recruited. Women with evidence of neurological disorder, recent head injury, pre-existing vascular disease, diabetes, renal disease, headache, and current vasoactive medication were excluded from the study.

Assessment of cerebrovascular haemodynamics was performed as soon as possible after the diagnosis of pre-eclampsia. Patients' age, height, body mass index (BMI), gestational age (in pregnant patients), and arterial pressure were recorded. Before recruitment into the study, all the patients were fully assessed by obstetricians and those with severe pre-eclampsia (diastolic arterial pressure greater than 110 mm Hg and/or evidence of hyper-reflexia) were admitted immediately for anti-hypertensive therapy and/or induction of labour, and could not therefore be included in the study. The pre-eclamptic patients who were admitted to the study underwent carotid ultrasound scan to exclude any significant carotid artery disease.

All pre-eclamptic subjects were followed-up at 6 and/or 12 weeks post-partum to ensure that their arterial pressure had returned to normal levels, proteinuria had cleared, and that they had not suffered any neurological problems at any time during their stay in hospital or thereafter.

Study set-up

All subjects were studied in the supine position. The pregnant women were positioned with 15° left-lateral tilt to minimize any aortocaval compression. The left middle carotid artery (MCA) was identified using a 2 MHz-pulsed TCD probe (SciMed PCDop 842), and the position of the probe was fixed with a headband to ensure a constant angle of insonation throughout the period of the study. TCD measurements were recorded onto digital audiotape for subsequent analysis using specific software (SciMed UK). Following application of a nose clip, constant end-tidal carbon dioxide (E'_{CO_2}) monitoring was instituted via a mouthpiece connected to a Datex Capnomac monitor. The arterial pressure was measured at 1-min intervals with a non-invasive arterial pressure monitor (Dynamap) for the duration of the test. Further monitoring included heart rate and oxygen saturation measurements using pulse oximetry.

Following a period of acclimatization to the study apparatus, each subject's baseline heart rate, arterial pressure, oxygen saturation, E'_{CO_2}, and MCAFV were recorded.

TCD data

Cerebral autoregulation was assessed by the transient hyperaemic response (THR) test.[12 13] This involved a 10-s compression of the ipsilateral common carotid artery (CCA) followed by sudden release of the compression, leading to hyperaemic flow in the MCA. Criteria for acceptance of a THR test were: (1) a sudden and maximal decrease in flow velocity at onset of the compression; (2) stable heart rate for the period of the compression; (3) steady TCD signal for the duration of the compression; and (4) absence of flow transients following release of the compression.

Two indices were used to analyse the THR test to assess autoregulation: the transient hyperaemic response ratio (THRR);[11] and the strength of autoregulation (SA).[12 13] To calculate these indices, three MCAFV waveforms were selected from the recordings during the THR test (Fig. 1): (1) the MCA waveform immediately before compression, F1; (2) the first waveform following compression, F2; and (3) the waveform immediately following release of compression, F3. The time-averaged mean of the outer envelope of the flow velocity profile was used for performing the analysis (Fig. 1). THRR was calculated as:[11]

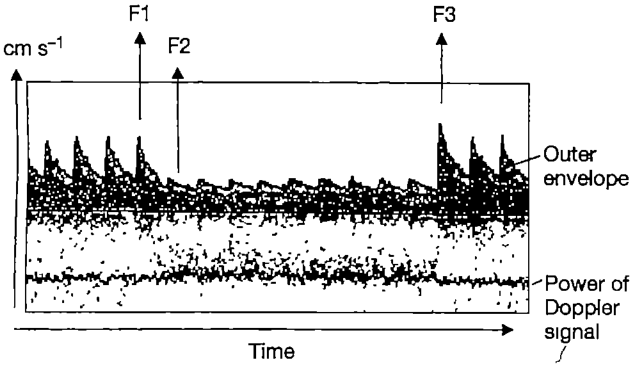


Fig 1 Example of the THR test. Baseline flow velocity (FV), F1, reduces to F2 at the onset of compression If autoregulation is effective, FV after the release of compression (F3) shows a hyperaemic response (i.e. F3>F1). The line below the MCAFV trace shows the reflected power of the Doppler signal; unchanged power during the test suggests stable conditions. For the measurement of FV, the time-averaged mean of the outer envelope is taken The outer envelope defines the upper limit of the frequency waveform for every pulse. It can be generated by computer (software by SciMed UK), and is shown as the continuous black line that joins the peaks of Doppler frequency spectrum during each cardiac cycle.

$$\mathrm{THRR=F3/F1}$$

SA was calculated as:[13]

$$\mathrm{SA=(F3\times P2)/(MAP\times F1)}$$

where P2 is the greater value of either the estimated arterial pressure in the MCA at the onset of CCA compression, as calculated by P2=MAP×F2/F1, or 60 mm Hg (the assumed lower limit of autoregulation). Details of the derivation of these formulae have been published elswhere.[12 13]

The compression ratio (CR), a measure of the magnitude of decrease in flow velocity during the compression, was calculated using the formula:[11]

$$\mathrm{CR\%=(F1-F2)\times(100/F1)}$$

$\mathrm{CRCO_2}$ was assessed by recording the MCAFV during induced hypocapnia (voluntary hyperventilation to an $\mathrm{E'_{CO_2}}$ of 1 kPa below baseline), and hypercapnia (addition of carbon dioxide to the inspired gases (oxygen-enriched air) to achieve an $\mathrm{E'_{CO_2}}$ of 1 kPa above baseline). $\mathrm{CRCO_2}$ was calculated as per cent change in MCAFV per kPa change in $\mathrm{E'_{CO_2}}$.

$$\mathrm{CRCO_2} = 100\times \frac{(\mathrm{MCAFV_{high\,CO_2}} - \mathrm{MCAFV_{low\,CO_2}})/\mathrm{MCAFV_{low\,CO_2}}}{\mathrm{E'_{CO_2\,high}} - \mathrm{E'_{CO_2\,low}}}$$

The eCPP and CrCP were calculated using the method described by Belfort and colleagues.[7]

Table 1 Physical characteristics of the patients. Values are as mean (SD or range) for age, height, and BMI, and median [interquartile range] for parity and gestation. *$P<0.05$ compared with non-pregnant group using ANOVA with Tukey's test

	Pre-eclamptic (n=30)	**Healthy pregnant** (n=30)	**Non-pregnant** (n=30)
Age (yr)	29.3 (19–40)	29.8 (18–41)	29.7 (18–42)
Height (cm)	164 (5)	164 (6)	165 (6)
BMI (kg m^{-2})	28 (8)*	26 (4)	24 (4)
Parity	0 [0–1]	0 [0–1]	–
Gestation (weeks)	37 [35–39]	37 [36–38]	–

$$\mathrm{eCPP = Velocity_{mean}} \times \frac{\mathrm{(MAP - DBP)}}{\mathrm{MCAFV_{mean} - MCAFV_{diastolic}}}$$

$$\mathrm{CrCP=MAP - eCPP}$$

Statistics

We calculated that 30 patients would be required in each of the three groups to detect a 20% difference in the SA across the groups with 90% power at alpha=0.05, assuming the coefficient of variation of SA to be approximately 10%. The coefficient of variation for SA was assumed because of lack of previous data in pregnant women.

All data sets were checked for normality of distribution using the Anderson–Darling test. For comparisons between groups, ANOVA with Tukey's test (for pairwise comparison) was used for parametric data, and Kruskal–Wallis test was used for non-parametric data. $P<0.05$ was used to denote statistical significance. Minitab Release 13.3 was used for all statistical analyses.

Results

Thirty-five women with pre-eclampsia were enrolled into the study. Two were not included because of obstetric intervention before completion was possible, two because we were unable to identify a suitable MCA signal, and one because we were unable to perform a satisfactory THR test. None of the pre-eclamptic patients had a carotid artery atheromatous plaque.

The characteristics of the three groups of women included in the study are shown in Table 1. The groups were comparable for distribution of age and height; parity and gestation in healthy pregnant patients were similar to pre-eclamptics. Compared with non-pregnant subjects, the BMI in pre-eclamptic patients was significantly higher ($P<0.05$).

Baseline values for arterial pressure and $\mathrm{E'_{CO_2}}$ for the three groups are shown in Table 2. The systolic, diastolic, and mean arterial pressures (MAP) were significantly higher in the pre-eclamptic group ($P<0.05$) as compared with the healthy pregnant and non-pregnant control groups. The baseline $\mathrm{E'_{CO_2}}$ levels in the pre-eclamptic and healthy

Table 2 Baseline data Values are mean (SD) $^*P<0.05$ compared with the other two groups using ANOVA with Tukey's test

	Pre-eclamptic (n=30)	Healthy pregnant (n=30)	Non-pregnant (n=30)
Systolic arterial pressure (mm Hg)	149 (12)*	120 (11)	121 (11)
Diastolic arterial pressure (mm Hg)	97 (10)*	76 (10)	77 (7)
MAP (mm Hg)	113 (11)*	90 (10)	89 (9)
E'_{CO_2} (kPa)	4.3 (0 4)	4.2 (0 4)	5.1 (0.4)*

Table 3 Cerebral haemodynamic measurements and calculated variables. Mean (SD) values of MCAFV, CR, THRR, SA, $CRCO_2$, eCPP, and CrCP are given $^*P<0\ 05$ compared with the other two groups using ANOVA with Tukey's test

	Pre-eclamptic (n=30)	Healthy pregnant (n=30)	Non-pregnant (n=30)
MCAFV (cm s^{-1})	67.9 (13 9)	56.7 (11.5)*	68 7 (14)
CR	32.3 (18 0)	34.9 (8 2)	34.3 (12 0)
THRR	1 68 (0 18)	1.64 (0.19)	1 57 (0.25)
SA	1.19 (0.29)	1 21 (0 19)	1.13 (0 20)
$CRCO_2$	26 6 (5 9)	27.7 (7.7)	28 0 (6 4)
eCPP (mm Hg)	65.4 (14 6)	60.3 (18.2)	43 3 (17.6)*
CrCP (mm Hg)	48 1 (16.1)	29 3 (20 1)*	44 5 (15.4)

pregnant groups were significantly lower than in the non-pregnant group ($P<0.05$).

The values of the cerebral haemodynamic variables are given in Table 3. Baseline MCAFV was significantly lower ($P<0.05$) in the healthy pregnant group compared with the pre-eclamptic and non-pregnant groups. There were no significant differences between the three groups for CR, THRR, SA, or $CRCO_2$. eCPP was significantly higher ($P<0.05$) in the pre-eclamptic and pregnant groups as compared with the non-pregnant control group. The CrCP was significantly lower in the healthy pregnant control group than the other two groups.

Discussion

We have shown that normal pregnancy is associated with a lower MCAFV as compared with non-pregnant women. However, MCAFV in pre-eclampsia is similar to that in non-pregnant women. The eCPP is higher in healthy pregnant women, as compared with non-pregnant women, and is maintained at this higher level during pre-eclampsia.

Changes in MCAFV

The effects of pregnancy and/or pre-eclampsia on MCAFV have been studied by other investigators. Ikeda and colleagues[3,5] found little change in mean MCAFV during the first two trimesters but reduced values in the third trimester. Williams and Wilson[4] showed that MCAFV fell significantly with advancing gestational age. In another study, Williams and Wilson[18] used TCD to assess cerebral haemodynamics in 17 non-pregnant women, 17 normotensive pregnant women, 20 pregnant women with pre-existing hypertension, and 21 pre-eclamptic women. The pregnant women were all in their third trimester. There was no difference in mean MCAFV in healthy pregnancy compared with non-pregnant women and a small, but non-significant, increase in mean MCAFV in the hypertensive and pre-eclamptic women. Demarin and colleagues[6] studied pre-eclamptic women before and after delivery and found a progressive increase in MCAFV during late pregnancy. Ohno and colleagues[19] compared MCAFV in 35 healthy pregnant and 17 pre-eclamptic women. In this study, the mean MCAFV was significantly higher in the pre-eclamptic group. It has been suggested that these increases in MCAFV are because of a degree of vasospasm. The differences between the findings of various studies with regards to the changes in MCAFV in pre-eclampsia might be explained by the differences in the severity of pre-eclampsia between the studies. Some investigators have reported increased MCAFV in symptomatic, compared with asymptomatic pre-eclamptics.[6,20,21]

In the present study, all our patients in the pre-eclampsia group were asymptomatic. We found that the values of MCAFV in pre-eclampsia, although similar to those in the non-pregnant group, were significantly higher than those seen in healthy pregnancy. These findings are in agreement with some of the previous reports.[3,5,6,19] Overall, it would appear that MCAFV falls with advancing gestational age. An increase in late pregnancy to a level equal to, or greater than, normal non-pregnant velocities is suggestive of pre-eclampsia and probable underlying vasospasm.

Cerebral autoregulation and carbon dioxide reactivity

As far as we are aware, there are no previously reported studies using TCD, which have looked specifically at the effects of pregnancy and/or pre-eclampsia upon cerebral autoregulation or $CRCO_2$. It has been generally assumed that cerebral autoregulation remains intact during healthy pregnancy as the increase in cerebral blood flow is limited despite the raised cardiac output.[1] With respect to pre-eclampsia, some investigators have suggested that the endothelial dysfunction seen in the pre-eclampsia/eclampsia syndrome may alter cerebral haemodynamics.[22]

Our study confirms that cerebral autoregulation remains intact in healthy pregnancy, as we found no significant differences in THRR, SA, or $CRCO_2$ between the non-pregnant and healthy pregnant groups. In addition, perhaps surprisingly, we found no difference in these variables in patients with pre-eclampsia. This may be because all our pre-eclamptic patients were asymptomatic, and therefore, can be supposed to have had only mild disease. None of the pre-eclamptic women we studied went on to suffer an eclamptic seizure. Our study procedure required a carotid ultrasound scan in the department of radiology before investigation of the patient's cerebral haemodynamics. We were therefore unable to investigate severe pre-eclamptics as they were either confined to the labour suite, or underwent urgent Caesarean section. The carotid ultrasound scan in pre-eclamptic patients was performed to rule out the presence of any atheromatous plaques in the internal carotid artery, which in theory, could be dislodged during carotid compression for the THR test. The risk of developing atheromatous disease in pre-eclampsia has not been reported. We decided to screen pre-eclamptic patients as a matter of precaution because hypertension is one of the risk factors for developing atheromatous disease. Patients from other groups were not screened because they did not have any of the risk factors associated with atheromatous disease.

CPP and CrCP

Some studies have investigated eCPP in pre-eclamptic patients. Williams and Wilson[18] found that mean eCPP was significantly lower in non-pregnant women compared with both healthy pregnant and (mild) pre-eclamptic women. Belfort and colleagues[22] suggested that the brain can be 'normally perfused, under-perfused or over-perfused' in pre-eclampsia. In a different study, Belfort and colleagues[20] also found that increasing severity of headache was associated with increasing eCPP.

We found a lower eCPP in non-pregnant women compared with healthy pregnant and pre-eclamptic women. There was no difference between healthy pregnancy and pre-eclampsia. These findings are similar to those of Williams and Wilson,[18] although the absolute values of eCPP in our study are different. Previously reported results by Belfort and colleagues,[20] would suggest that the majority of the pre-eclamptics in our study had mild disease. The interpretation of the results of our study in conjunction with the previous studies, [18 20–22] would suggest that pregnancy leads to an increase in eCPP, with further increases in symptomatic, but not severe pre-eclampsia.

The only previously published data on cerebral CrCP in pregnancy comes from Belfort and colleagues[7] in a study of the effects of nimodipine and magnesium on eCPP in pre-eclampsia. They found that magnesium increased, and nimodipine reduced CrCP. Our data suggest that CrCP is reduced in the latter stages of healthy pregnancy, compared with non-pregnant women. This results in increased eCPP in healthy pregnancy despite an unchanged MAP. However, in pre-eclampsia the CrCP increases, probably as a result of increased vascular tone, so that despite a significant increase in MAP, the level of eCPP remains unchanged.

What is the clinical significance of our results? As cerebral autoregulation and $CRCO_2$ are preserved in healthy pregnancy and in asymptomatic pre-eclampsia, these groups of patients should be able to tolerate moderate changes in E'_{CO_2} or MAP under anaesthesia. Healthy pregnancy is associated with increased eCPP, which is a result of a decrease in downstream CrCP. In pre-eclampsia, an increase in MAP is also associated with an increase in downstream pressure, therefore CPP is maintained. The hypotensive agents used in pre-eclampsia may affect CrCP in varying manner. It would be logical to use agents that affect MAP and CrCP in a similar fashion so the CPP is maintained. Therapies that reduce MAP but not CrCP will reduce cerebral perfusion. Further work needs to be done in this field, both to study the effects of severe/symptomatic pre-eclampsia upon the cerebral circulation, and the effects of the various anti-hypertensive drugs used in its treatment.

Acknowledgement

This study was funded by a grant from the Obstetric Anaesthetist's Association.

References

1 Descamps P, Marret H, Binelli C, Chaplot S, Gillard P Body changes during pregnancy. *Neurochirurgie* 2000; **46**: 68–75

2 Kim TH, Weiner CP, Thompson LP. The effect of pregnancy on contraction and endothelium-mediated relaxation of renal and mesenteric arteries. *Am J Physiol* 1994; **267**: 41–7

3 Ikeda T, Ikenoue T, Mori N, *et al.* Effect of early pregnancy on maternal regional cerebral blood flow. *Am J Obstet Gynecol* 1993, **168**: 1303–8

4 Williams K, Wilson S. Maternal middle cerebral artery blood flow velocity variation with gestational age. *Obstet Gynecol* 1994; **84**: 445–8

5 Ikeda T, Mori N. Assessment of cerebral haemodynamics in pregnant women by internal carotid artery pulsed Doppler velocimetry. *Am J Obstet Gynecol* 1990, **163**: 494–8

6 Demarin V, Rundek T, Hodek B. Maternal cerebral circulation in normal and abnormal pregnancies. *Acta Obstet Gynecol Scand* 1997; **76**: 619–24

7 Belfort MA, Saade GR, Yared M, *et al.* Change in estimated cerebral perfusion pressure after treatment with nimodipine or magnesium sulphate in patients with preeclampsia. *Am J Obstet Gynecol* 1999; **181**: 402–7

8 Ramanathan J, Angel JJ, Bush AJ, Lawson P, Sibai B. Changes in maternal cerebral artery blood flow velocity associated with general anaesthesia in severe preeclampsia. *Anesth Analg* 1999; **88**: 357–62

9 Matta BF, Lam AM, Strebel S, Mayberg TS. Cerebral pressure autoregulation and carbon dioxide reactivity during propofol-induced EEG suppression. *Br J Anaesth* 1995; **74**. 159–73

10 Giller CA. A bedside test for cerebral autoregulation using transcranial Doppler ultrasound. *Acta Neurochir* 1991; **108**: 7–14

11 Smielewski P, Czosnyka M, Kirkpatrick P, McEroy H, Rutkowska H, Pickard JD. Assessment of cerebral autoregulation using carotid artery compression. *Stroke* 1996; **27**: 2197–203

12 Mahajan RP, Cavill G, Simpson EJ, Hope DT. In Klingelhofer J (ed.) *New Trends in Cerebral Haemodynamics and Neurosonology.* Amsterdam: Elsevier Science BV, 1997; 618–23

13 Mahajan RP, Cavill G, Simpson EJ. Reliability of the transient hyperemic response test in detecting changes in cerebral autoregulation induced by the graded variations in end-tidal carbon dioxide. *Anesth Analg* 1998; **87**. 843–9

14 Czosnyka M, Smielewski P, Piechnik S, *et al.* Critical closing pressure in cerebrovascular circulation. *J Neurol Neurosurg Psychiatry* 1999; **66**: 606–11

15 Dernbach PD, Little JR, Jones SC, Ebrahim ZY. Altered cerebral autoregulation and CO_2 reactivity after aneurysmal subarachnoid hemorrhage. *Neurosurgery* 1988; **22**: 822–6

16 Lovick AH, Pickard JD, Goddard BA. Prediction of late ischaemic complications after cerebral aneurysm surgery—use of a mobile microcomputer system for the measurement of pre-, intra- and postoperative cerebral blood flow. *Acta Neurochir* 1982; **63**: 37–42

17 Pickard JD, Matheson M, Patterson J, Wyper D. Prediction of late ischemic complications after cerebral aneurysm surgery by the intraoperative measurement of cerebral blood flow. *J Neurosurg* 1980; **53**: 305–8

18 Williams KP, Wilson S. Variation in cerebral perfusion pressure with different hypertensive states in pregnancy. *Am J Obstet Gynecol* 1998; **179**: 1200–3

19 Ohno Y, Kawai M, Wakahara Y, Kitagawa T, Kakihara M, Arii Y. Transcranial assessment of maternal cerebral blood flow velocity in patients with pre-eclampsia. *Acta Obstet Gynecol Scand* 1997; **76**: 928–32

20 Belfort MA, Saade GR, Grunewald C, *et al.* Association of cerebral perfusion pressure with headache in women with pre-eclampsia. *Br J Obstet Gynaecol* 1999; **106**: 814–21

21 Zunker P, Ley-Pozo J, Louwen F, Schuierer G, Holzgreve W, Ringelstein EB. Cerebral haemodynamics in pre-eclampsia/eclampsia syndrome. *Ultrasound Obstet Gynecol* 1995; **6**: 411–5

22 Belfort MA, Grunewald C, Saade GR, Varner M, Nisell H. Preeclampsia may cause both overperfusion and underperfusion of the brain: a cerebral perfusion based model. *Acta Obstet Gynecol Scand* 1999; **78**: 586–91

British Journal of Anaesthesia **89** (5): 693–6 (2002)

Fluoride excretion in children after sevoflurane anaesthesia

C. Lejus[1]*, C. Le Roux[1], E. Legendre[1], M. Renaudin[1], H. L. Boiteau[2] and M. Pinaud[1]

[1]Department of Anaesthesiology, Hôtel Dieu, C.H.U. Nantes, France. [2]Société d'Etude des Risques Toxiques, Nantes, France

**Corresponding author: Service d'Anesthésie et de Réanimation Chirurgicale, Hôtel - Dieu, F-44093 Nantes Cedex 01, France*

Background. Defluorination of sevoflurane is catalysed by the hepatic enzyme cytochrome P450 2E1 (CYP2E1). Data about the ontogenesis (developmental variations in activity) of this enzyme suggest a low metabolism of sevoflurane during the first months of life.

Methods. To test this hypothesis, 45 children less than 48 months of age undergoing sevoflurane anaesthesia were enrolled in a prospective open clinical trial. The 24 h urine fluoride excretion was measured in five groups of children (A, <4 months; B, 4 to <8 months; C, 8–12 months; D, >12–24 months; and E, >24–48 months old). An index of sevoflurane metabolism (ISM) was calculated as the ratio of fluoride excretion, cumulative expiratory sevoflurane concentrations measured every minute during anaesthesia, and body surface area. ISM values were median (IQ 25–75%).

Results. ISM was lower in group A (n=9, 18.9 (11.2–29.5) than group C (n=11, 44.2 (37.5–53.5), P<0.05), group D (n=7, 52.6 (45.8–68.4), P<0.01) and group E (n=9, 53.6 (50.7–85), P<0.001). Median ISM expressed as a function of median age, exponentially increased with a rapid increase during the first months of life, followed by a slower increase after 10 months of age.

Conclusion. These results suggest that, in children less than 48 months, sevoflurane metabolism parallels postnatal development of CYP2E1.

Br J Anaesth 2002; **89**: 693–6

Keywords: anaesthetics volatile, sevoflurane; children; kidneys, urine; metabolism, sevoflurane

Accepted for publication: June 17, 2002

Sevoflurane is a volatile halogenated gas, widely used for the induction and maintenance of anaesthesia in children.[1] Sevoflurane 2–5% undergoes hepatic biotransformation to inorganic fluorides and hexafluoroisopropanol (HFIP).[2] Fluorides peak in the plasma within 30 min of the end of sevoflurane administration and are eliminated in the urine.[3] Cytochrome P450 2E1 (CYP2E1) is the major liver enzyme catalysing defluorination of sevoflurane,[4] and accounts in adults for 1–10% of total hepatic CYP proteins.[5] However, its activity is very low during the neonatal period, increasing during the first hour after birth and then gradually increases during the first year of life to reach the adult value in children aged 1–10 yr.[6] The data suggest a lower rate of defluorination of sevoflurane would occur in small children than in adults.

This study was undertaken to explore the effect of age on the metabolism of sevoflurane in small children, by measuring the postoperative fluoride urinary excretion.

Methods

After institutional human investigation committee approval and informed parental consent, 45 (11 female/34 male) children ASA physical status I or II, less than 48 months of age undergoing anaesthesia by inhalation of sevoflurane during elective surgery, were enrolled in this prospective, open, non-randomized clinical trial. Children with impairment of hepatic, cardiac or renal function, or those receiving propofol during induction or maintenance, were not included in the study. Children older than 5 months were given oral or rectal midazolam 0.3 mg kg^{-1}, 20 min before anaesthesia that was induced by inhalation of sevoflurane 7% in nitrous oxide/oxygen ($F\text{I}_{\text{O}_2}$=0.5). After i.v. catheter-

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Table 1 Physical characteristics of the patients. Results are medians (interquartile range 25–75%). BSA, body surface area. Exposure corresponds to the sum of expiratory sevoflurane concentrations measured every minute during anaesthesia. ISM was calculated as indicated in the data analysis section. Comparison between groups by Kruskal–Wallis analysis compared with group A: $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$, compared with group E: $^{\#}P<0.05$

	Group (*n*)				
	A (9)	B (9)	C (11)	D (7)	E (9)
Age (months)	2.4 (2–3.2)	5.1 (4–7.5)	9 (8.2–9.5)	18.3 (16–21.5)	28.7 (28–38)
Weight (kg)	4.9 (4.2–5.7)	6.7 (6.5–7.5)	9 (8.7–9.9)	12 (10.5–12.2)	13.5 (13–15)
BSA (m^2)	0.28 (0.25–0.31)	0.35 (0.34–0.38)	0.43 (0.42–0.47)	0.54 (0.49–0.55)	0.59 (0.57–0.65)
Sex (F/M)	2/9	1/8	1/10	3/4	3/6
Duration of anaesthesia (min)	96 (68–190)	166 (100–215)	163 (147–204)	130 (91–160)	123(117–157)
Exposure (% min)	215 (193–339)	301 (246–435)	405 (334–493)	293 (177–398)	339 (250–343)
Exposure (MAC_{hours})	1.19 (1.07–1.88)	1.79(1.46–2.55)	2.41(1.99–2.94)	1.88 (1.13–2.55)	2.17(1.6–2.29)
Urinary fluoride concentration (μmol $litre^{-1}$)	33.5 (30.4–42)	105 (79–155)	116 (91.9–145)*	156 (108–166.3)**	121 (104–174.6)***
ISM (% μmol $\%^{-1}$ min^{-1} m^{-2})	18.9 (11.2–29.5)	26.9 (21.4–48.1)$^{\#}$	44.2 (37.5–53.5)*	52.6 (45.8–68.4)**	53.6 (50.7–85)***

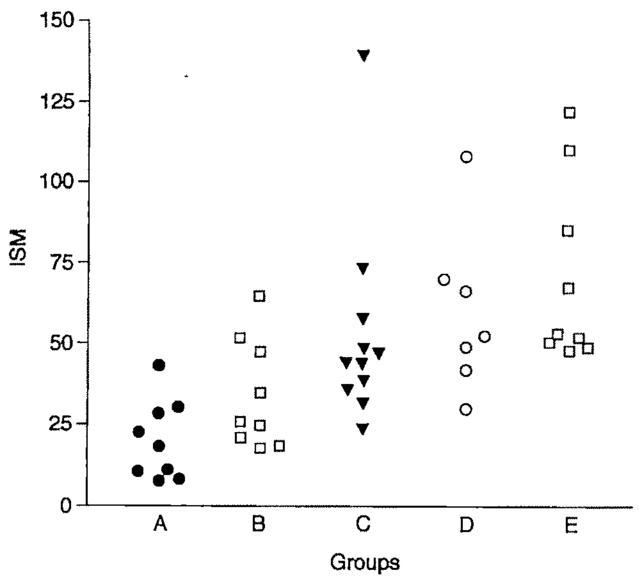


Fig 1 Individual points (n=45) for the ISM, groups A (<4 months), B (4 to <8 months), C (8–12 months), D (>12–24 months), and E (>24 months)

ization, dextrose 1% isotonic sodium chloride was infused peroperatively at 25 ml kg^{-1} during the first hour, then 83 ml h^{-1} m^{-2}. The airway was managed with a laryngeal mask or tracheal tube as indicated by the surgery. No neuromuscular blocking agent was administered. Sevoflurane administration was adjusted as clinically indicated. Immediately after induction of anaesthesia, i.v. acetaminophen 30 mg kg^{-1} was administered and followed by 15 mg kg^{-1} orally every 6 h. Intra-operative analgesia was given intravenously or by regional anaesthesia performed before the surgical incision. For postoperative analgesia, intermittent i.v. nalbuphine 0.2 mg kg^{-1} or continuous i.v. morphine 20–40 μg kg^{-1} h^{-1} was used. Dextrose 5% infusion (83 ml h^{-1} m^{-2}) with electrolytes was used postoperatively until the patient was able to eat normally.

The bladder was emptied after induction of anaesthesia by manual abdominal pressure. If a urinary catheter was not required, a bag was stuck on the skin for urinary collection during the first 24 h after the beginning of sevoflurane anaesthesia. The child was only included in the study at the time of the urine collection if no urine leakage was observed during this period. It was necessary to screen 70 children before definitively including 45 patients in the study because of urine leakage during the 24-h urine collection.

After mixing and measuring the 24-h urine collection, a sample was frozen at –20°C until measurement of fluoride concentration. The fluoride urine concentrations were determined with an ion-selective electrode.[7] Its performance was checked by an Interlaboratory Control program, managed by the Canadian toxicologic centre in Quebec (CHUQ, Sainte-Foy). The intra-essay coefficient of variation was 1.24, 0.21 and 0.48% for fluoride concentrations of 13, 53, and 133 μM, respectively. The inter-essay coefficient of variation was 4 and 4.2% for fluoride concentrations of 64 and 223 μM, respectively.

The ISM was calculated using the urinary fluoride excretion during the first 24 h, the exposure to sevoflurane, and the body surface area, as follows:

$$ISM=100\times(F\times U)/(E\times S)$$

with F being urine fluoride concentration (μm $litre^{-1}$), U being 24-h urine volume (litre), E being exposure to sevoflurane (% min), and S being body surface area (m^2) [calculated using $(4W+7)/(W+90)$, where W is weight (kg)].

The exposure to sevoflurane (E) was estimated by the sum of the expiratory sevoflurane concentrations that were measured every minute during sevoflurane administration. Measurements were made using an infra-red based, multigas module (SAM module, Marquette electronics™, Milwaukee, USA) and sidestream sampling with a flow rate of 250 ml min^{-1}. Rise time (delay before automatic return to zero to avoid contamination of measurement by

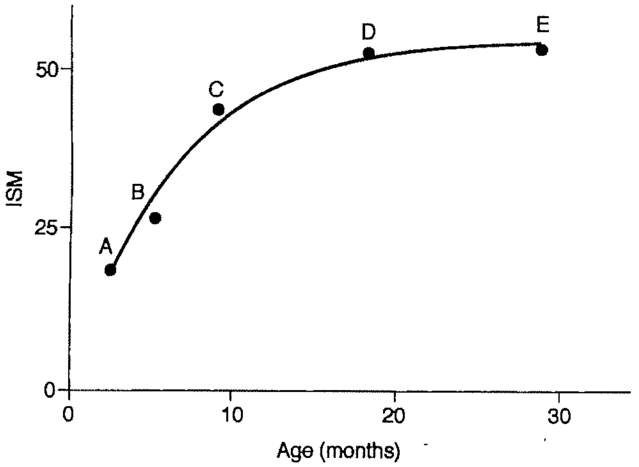


Fig 2 Relation between the median values of the ISM and the median values of age (months) in groups A (n=9, <4 months), B (n=9, 4 to <8 months), C (n=11, 8–12 months), D (n=7, >12–24 months), and E (n=9 >24 months). ISM was calculated as indicated in the data analysis section Non-linear regression ($ISM=55\,e^{-0.1575\,\text{age}}$, R^2=0.98)

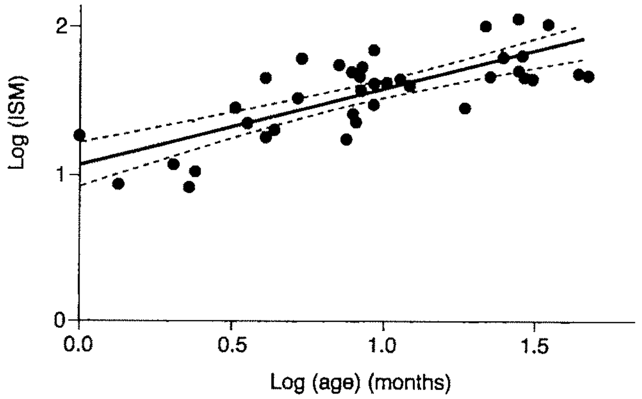


Fig 3 Double logarithmic transformation of age and ISM Linear regression analysis (R^2 0.59) of 45 individual points with slope 0.52 (0.07) and y-axis intercept=1.09 (0.07).

previous sampling) was less than 600 ms and the accuracy equal to 5% of the reading.

Data are expressed as medians (interquartile range 25–75%). The ISM were compared in five groups of children (A, <4 months of age; B, 4 to <8 months; C, 8–12 months; D, >12–24 months; and E, >24 months) using Kruskal–Wallis analysis of variance. P<0.05 was considered statistically significant. If P was significant, Kruskal–Wallis analysis was followed by a Dunn's multiple comparison test.

Statistical analysis was performed on the Statview® 4.5 software (Abacus Concepts Inc., Berkeley, CA, USA). A relation between the median values of ISM and the age of each group was searched for by non-linear regression analysis using Prism, version 3.02 (Graph Pad software Inc.).

Results

The physical characteristics of the patients are given in Table 1. No significant differences between groups in exposure to sevoflurane (duration of anaesthesia, real cumulative exposure, or MAC_{hour} exposure) were found (Table 1). Median expiratory concentration was 2.3 (1.9–2.7)%. Fluoride urine 24 h concentrations and ISM varied in the five groups: the younger the children, the lower the ISM values. Individual data for ISM are shown in Figure 1. The relationship between age and ISM was best predicted by non-linear manipulation. The plot of median ISM as a function of the median age for each group, showed an exponential increase in ISM with age, with a curve linearity suggesting an allometric model (i.e. a linear relation between ISM and age after double logarithmic transformation) (Fig. 2). To confirm this hypothesis, median and individual values of age and ISM were normalized by double logarithmic transformation. Thereafter, median values of ISM and age were highly correlated by linear regression analysis (R^2 0.98). The plot of individual data of ISM and age after allometric transformation (Fig. 3) also showed a linear relationship, despite a lower correlation coefficient, that was explained by the interindividual variability.

Discussion

The natural log relationship of fluoride urinary excretion to age after sevoflurane anaesthesia in small children, suggests an allometric evolution of the metabolism of sevoflurane during the three first years of life, characterized by a low sevoflurane metabolism during the first 3 months, followed by an increase in the rate of defluorination until 10 months of age. Allometry is used to describe the change in relative size of two physiological variables during growth or evolution.[8] It is frequently observed in the evolution of an organism's morphology and means that the variations during development of physiological variables are linearly related only after double logarithmic transformation. Such a relationship between ISM and age suggests that sevoflurane metabolism parallels postnatal development of CYPE21.

Data concerning the metabolism of sevoflurane in children are limited to two previous studies.[3 9] Those findings were correlated with our study: they have, respectively, shown smaller plasma fluoride peaks between 1 and 6 months,[3] and a lower area under the curve of plasma fluoride in children aged from 1 to 12 yr,[9] than in adults.

Fluoride production is related both to the administered dose of sevoflurane and to the CYP2E1 level activity.[10] Fluoride urinary excretion probably reflects more accurately the fluoride production than plasma concentrations, and has been used to demonstrate the role of CYP2E1 in the hepatic biotransformation of sevoflurane.[11] However, the use of urinary excretion standardized to sevoflurane exposure and body surface area in this study is original and has not been validated previously. The concept was guided by the need to take into account both variable exposures to sevoflurane, and physiological variables that are better indexed to body surface area than to body weight.

A limitation of our conclusion is the existence of extrahepatic metabolism of sevoflurane,[12] explained by the expression of CYP2E1 in the lung, small intestine, and brain, albeit to a lesser extent than in the liver.[5] In human hepatic microsomes, the rate of defluorination of sevoflurane has been shown to be well-correlated with liver CYP2E1 activity and selective inhibition.[4]

One of the clinical implications of the present study is that sevoflurane is the first substrate of CYP2E1 that could be used as an *in vivo* probe of its activity in children. Until now, chlorzoxazone, a centrally acting neuromuscular blocking agent, remained the only *in vivo* probe for CYP2E1 phenotyping in adults.[13] Because of the absence of pharmacological data, its safety in childhood has not been established. Several factors regulate CYP2E1 activity. Developmental expression is one of the keys factors. CYP2E1 is absent or barely detectable in the fetal liver, developing post-natally. Ontogenesis relates to the developmental variation in enzyme activity during growth. Knowledge of the ontogenesis of CYP2E1 resulted from *in vitro* studies using post-mortem liver samples from children of varying postnatal age.[6] Further implications of the immature metabolism of sevoflurane in infants and small children relate to nephrotoxicity from fluoride production.

More than 100 specific exogenous substrates of CYP2E1 have been identified, in addition to a number of endogenous ones.[5 14] Low CYP2E1 activity could be protection against the toxicity of drugs or compounds that undergo activation by CYP2E1 to produce metabolites that are cytotoxic or genotoxic, such as halothane and acetaminophen. Oxidative hepatic metabolism of halothane by CYP2E1 mediates an immune-based fulminant hepatic necrosis, because of the production of a reactive trifluoroacetyl halide.[15] The lower incidence of this rare but fatal side-effect in children,[16] rather than in adults, could be explained by a lower CYP2E1 activity. The toxicity of acetaminophen is related to its transformation by CYP2E1 in presence of overdose or hepatic gluthation depletion, to a toxic metabolite identified as *N*-acetyl-*p*-benzoquinone imine.[17] In mice, this toxicity is delayed, if expression of the CYP2E1 is lacking.[18] Pretreatment by propylene glycol, that inhibits CYP2E1, also prevents hepatic necrosis.[17] It is generally accepted that children are less susceptible than adults to acetaminophen toxicity because of developmental differences in its metabolism.[19] One of these differences could be a lower CYP2E1 activity.

In conclusion, the allometric variation of fluoride excretion after sevoflurane anaesthesia during the first years of life, confirms previous *in vitro* data about CYP2E1 ontogenesis.

Acknowledgement

This study was supported in part by a grant from Abbott-France.

References

1 Lerman J. Sevoflurane in pediatric anesthesia. *Anesth Analg* 1995; **81**: S4–10

2 Kharasch ED, Armstrong AS, Gunn K, Artru A, Cox K, Karol MD. Clinical sevoflurane metabolism and disposition. II. The role of cytochrome P4502E1 in fluoride and hexafluoroisopropanol formation. *Anesthesiology* 1995; **82**: 1379–88

3 Lerman J, Sikich N, Kleinman S, Yentis S. The pharmacology of sevoflurane in infants and children. *Anesthesiology* 1994; **80**: 814–24

4 Kharasch ED, Thummel KE. Identification of cytochrome P450 2E1 as the predominant enzyme catalyzing human liver microsomal defluorination of sevoflurane, isoflurane, and methoxyflurane. *Anesthesiology* 1993; **79**: 795–807

5 Lieber CS. Cytochrome P-4502E1: its physiological and pathological role. *Physiol Rev* 1997; **77**: 517–44

6 Vieira I, Sonnier M, Cresteil T. Developmental expression of CYP2E1 in the human liver. Hypermethylation control of gene expression during the neonatal period. *Eur J Biochem* 1996; **238**: 476–83

7 Fry BW, Taves DR. Serum fluoride analysis with the fluoride electrode. *J Lab Clin Med* 1970; **76**: 1020–5

8 Borland LM. Allometric determination of the distance from the central venous pressure port to wedge position of balloon-tip catheters in pediatric patients. *Crit Care Med* 1986; **14**: 974–6

9 Levine MF, Sarner J, Lerman J, *et al.* Plasma inorganic fluoride concentrations after sevoflurane anesthesia in children. *Anesthesiology* 1996; **84**: 348–53

10 Wandel C, Neff S, Keppler G, *et al.* The relationship between cytochrome P4502E1 activity and plasma fluoride levels after sevoflurane anesthesia in humans. *Anesth Analg* 1997; **85**. 924–30

11 Kharasch ED, Armstrong AS, Gunn K, Artru, Cox K, Karol MD. Clinical sevoflurane metabolism P450 in fluoride and hexafluoroisopropanol formation. *Anesthesiology* 1995; **82**: 1379–88

12 Van Obbergh LJ, Verbeeck RK, Michel I, Lim S, Veyckemans F. Extrahepatic metabolism of sevoflurane in children undergoing orthotopic liver transplantation. *Anesthesiology* 2000; **92**: 683–6

13 Bachmann K, Sarver JG. Chlorzoxazone as a single sample probe of hepatic CYP2E1 activity in humans. *Pharmacology* 1996; **52**: 169–77

14 Carriere V, Berthou F, Baird S, Belloc C, Beaune P, de Waziers I. Human cytochrome P450 2E1 (CYP2E1): from genotype to phenotype. *Pharmacogenetics* 1996; **6**: 203–11

15 Spracklin DK, Hankins DC, Fisher JM, Thummel KE, Kharasch ED. Cytochrome P450 2E1 is the principal catalyst of human oxidative halothane metabolism *in vitro*. *J Pharmacol Exp Ther* 1997; **281**: 400–11

16 Warner LO, Beach TP, Garvin JP, Warner EJ. Halothane and children: the first quarter century. *Anesth Analg* 1984; **63**: 838–40

17 Thomsen MS, Loft S, Roberts DW, Poulsen HE. Cytochrome P4502E1 inhibition by propylene glycol prevents acetaminophen (paracetamol) hepatotoxicity in mice without cytochrome P4501A2 inhibition. *Pharmacol Toxicol* 1995; **76**: 395–9

18 Lee SS, Buters JT, Pineau T, Fernandez-Salguero P, Gonzalez FJ. Role of CYP2E1 in the hepatotoxicity of acetaminophen. *J Biol Chem* 1996; **271**: 12063–7

19 Penna A, Buchanan N. Paracetamol poisoning in children and hepatotoxicity. *Br J Clin Pharmacol* 1991; **32**: 143–9

British Journal of Anaesthesia **89** (5): 697–701 (2002)

Is morphine-induced sedation synonymous with analgesia during intravenous morphine titration?

X. Paqueron[1]*, A. Lumbroso[1], P. Mergoni[1], F. Aubrun[1], O. Langeron[1], P. Coriat[1] and B. Riou[1 2]

[1]*Department of Anaesthesiology and Critical Care and* [2]*Department of Emergency Medicine and Surgery, Centre Hospitalier Universitaire Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris (AP-HP), Université Pierre et Marie Curie, Paris, France*

**Corresponding author: Département d'Anesthésie et de Réanimation, Centre Hospitalier Universitaire Pitié-Salpêtrière, 47 Boulevard de l'Hôpital, F-75651 Paris Cedex 13, France*

Background. Postoperative morphine titration frequently induces sedation. The assumption is made that patients sleep when their pain is relieved. Some patients complain of persistent pain when they awake. We studied the time-course of sedation and analgesia to understand the determinants of patients' sleep during morphine titration.

Methods. Seventy-three patients requiring morphine titration in a post-anaesthetic care unit after major surgery, were studied. Fifty-two patients slept (Sleep group) and 21 did not (Awake group). When a patient slept during titration, morphine was discontinued. Visual analogue pain scale (VAS), Ramsay score (RS), and the bispectral index (BIS) were recorded at the beginning of titration (STonset), at sleep onset (STsleep), then 5, 10, 20, and 30 min afterwards (ST4).

Results. In the Sleep group, mean (SD) RS increased from 1.7 (0.4) to 2.4 (0.6) ($P<0.05$ *vs* STonset) and BIS decreased from 95 (5.0) to 89.8 (10.2) between STonset and STsleep ($P<0.05$), RS remained stable thereafter. Conversely, RS and BIS remained unaltered in the Awake group. The reduction in VAS was comparable between groups (from 78 (17) to 39 (21), and from 64 (16) to 30.4 (11), respectively). Even though mean (SD) VAS was 39 (21) at ST4 in the Sleep group, 13 patients (25%) maintained a VAS above 50 mm.

Conclusion. We observed dissociated effects of morphine on the time-course of sedation and analgesia with sedation occurring first, followed by analgesia. Therefore, morphine-induced sedation should not be considered as an indicator of an appropriate correct level of analgesia during i.v. morphine titration.

Br J Anaesth 2002; **89**: 697–701

Keywords: analgesia; analgesics opioid, morphine; monitoring, bispectral index; sedation

Accepted for publication: May 25, 2002

Treatment of postoperative pain in the post-anaesthesia care unit (PACU) mainly relies on morphine titration, as it provides efficient and rapid onset of analgesia.[1] Although the optimal dose of morphine is still a matter of debate, the usual recommendations for morphine titration include a short interval between two boluses (5–7 min) and no upper limit for the total administered dose.[2 3] Among morphine-induced side-effects, sedation occurs in up to 60% of cases during morphine titration, and represents a common cause of discontinuation of titration for reasons of safety.[3] The assumption is usually made that patients sleep when their pain has been relieved. Nevertheless, some patients complain of persistent pain when they awake and morphine titration is frequently resumed. Thus, sedation might not be synonymous with analgesia, and might even prolong the time to efficient pain relief, leading to extended stays in PACU.

Several behavioural scales assess depth of sedation. Among them, the Ramsay score (RS) is a validated and widely used technique.[4] Nevertheless, its components are somewhat subjective, and prone to observer bias. The use of this scale is easy, for it does not require any device, but its accuracy in detecting deep sedation is questionable during the early postoperative period. Many patients in PACU are

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

known to keep their eyes closed without being sedated. This corresponds to an RS of 3 in an apparently sleepy patient, leading to morphine discontinuation for safety reasons, independent of the visual analogue score (VAS) for pain.[3] Therefore, we attempted to find methods measuring the depth of sedation in a way that avoids the observer interpretation of the RS and of the patient's behaviour. The bispectral index (BIS) is a parameter derived from the electroencephalogram and has been validated in the assessment of the depth of anaesthesia[5] and the depth of sedation in the intensive care unit.[6 7] We felt that, as the technique is based on an analysis of electrical cortical activity, it could also provide a useful tool to assess the level of consciousness in awake patients. The BIS could also be useful to assess sedation in PACU, for it provides continuous information in contrast with the discontinuous assessment of behavioural scales.

Therefore, the current study was undertaken to provide a better assessment of the determinants of patient sedation during i.v. morphine titration in PACU, particularly in relation to the time-course of sedation and analgesia. The main goals of the study were to assess prospectively the temporal relationship between morphine titration, analgesia and sedation and to determine whether patients who sleep during i.v. morphine titration are simply sedated or are actually relieved from their pain.

Methods

After institutional review board approval (CCPPRB Pitié-Salpêtrière), 73 patients admitted to the PACU after major orthopaedic or urological surgery under general anaesthesia, and who required i.v. morphine titration were studied. A list of surgical procedures considered as highly painful was established (i.e. spine fusion, total knee arthroplasty, total hip arthroplasty, ligamentoplasty, major shoulder surgery, pelvic surgery, total nephrectomy, and radical abdominal prostatectomy) before the study.

Regional anaesthesia was an exclusion criterion. Anaesthetic and postoperative analgesic procedures were not standardized and were left to the discretion of the attending anaesthetists in charge of the patient, according to local procedures.[3] The only constraints placed upon anaesthetists were to use only sufentanil as the intraoperative opioid, and isoflurane as the volatile anaesthetic. Postoperative analgesia consisted mainly of a combination of propacetamol and ketoprofen (when not contraindicated) and morphine.

Local procedure for morphine titration

According to our local procedure,[3] morphine titration was initiated when the pain VAS was higher than 30 mm on a 100 mm scale. Patients received oxygen via a facial mask at the rate of 5 litre min^{-1}. Boluses of i.v. morphine were 3 or 2 mg when patient's weight was above or below 60 kg, respectively. The interval between boluses was 5 min, without an upper dose limit. Morphine titration was discontinued when VAS was inferior to 30 mm, in case of side-effects such as nausea and/or vomiting, respiratory depression (Sp_{O_2} <92%, ventilatory frequency rate <10), or occurrence of deep sedation (eyes closed >3 min, RS >2). An RS on a 6-point scale was used (1=anxious and agitated patient; 2=cooperative patient; 3=asleep patient, brisk response to loud voice; 4=asleep patient, sluggish response to loud voice; 5=no response to loud voice; score of 6=no response to pain).

Among the 73 patients included, there was a group of patients who slept (Sleep group: eyes closed >3 min, RS >2) in whom i.v. morphine was discontinued, and a group of patients who did not sleep (Awake group). Morphine was not discontinued in the Awake group. The Awake group was designed to serve as a control group to assess the quality of BIS monitoring and to compare BIS and electromyographic (EMG) changes among patients who slept and those who stayed awake.

All patients were observed using a BIS monitor (A-2000 monitor; Aspect MS®, Leiden, The Netherlands). When a patient slept while receiving morphine, its administration was discontinued. The following variables were recorded: BIS value, RS, VAS, arterial oxygen saturation (Sp_{O_2}), ventilatory frequency (VF), and the EMG recorded on the BIS monitor. We proceeded in the following order. First, the BIS and EMG values were recorded when the patient was asleep. Then, the patient was awoken and we assessed the RS. Finally, the VAS for pain was scored. After this, the patient usually fell asleep again. In the Sleep group, these variables were assessed just before the onset of titration (STonset), when patients started to sleep (STsleep), then 5 (ST1), 10 (ST2), 20 (ST3), and 30 min (ST4) after the onset of sleep. In the Awake group, the same variables were recorded just before the onset of titration (ATonset), then at 5 (AT0), 10 (AT1), 20 (AT2), 30 min (AT3), and at the end of titration (AT4).

Duration of surgery, total intraoperative sufentanil dose, administration of propacetamol and of ketoprofen, delay between tracheal extubation and onset of morphine titration, total dose of morphine administered, body temperature at onset of morphine titration and time of sleep after morphine titration were also measured.

Data are expressed as mean (SD), or as median and its 95% confidence interval when variables were not normally distributed (duration of surgery, delay between extubation, and onset of morphine titration). Continuous variables (age, weight, cumulative doses of sufentanil, total dose of morphine administered) were analysed using the Student's *t*-test. Comparison of two medians was performed using the Mann–Whitney test. Changes in VAS, BIS, Sp_{O_2}, ventilatory frequency, and EMG were analysed using an analysis of variance for repeated measures and a Bonferroni correction. The RS was analysed using Kruskall–Wallis test. Comparison of two numbers was performed using the chi-squared test. All *P* values were two-tailed and a *P* value of <0.05 was considered significant. Analyses were performed on a computer using NCSS 6.0 software (Statistical Solutions Ltd., Cork, Ireland).

Results

Seventy-three consecutive patients admitted to the PACU after major orthopaedic or urological surgical procedures and who received an i.v. morphine titration were studied. Among these patients, 52 slept (Sleep group) during morphine titration and 21 did not (Awake group).

Table 1 Patients characteristics. Values are mean (SD or range) {and per cent} or median and [95% confidence interval] **P*<0.05 *vs* Sleep group

	Sleep group (*n*=52)	**Awake group (*n*=21)**
Age (yr)	53 (19–85)	53 (25–88)
Weight (kg)	70 (13)	70 (16)
Female (%)	31 {60}	5 {24}*
Male (%)	21 {40}	16 {76}*
Urological procedures		
Radical abdominal prostatectomy	3	6
Nephrectomy	4	2
Orthopaedic procedures		
Spine fusion	11	3
Upper limb	3	1
Lower limb	31	9
Duration of surgery (min)	170 [60–275]	110 [60–175]*
Intraoperative sufentanil dose (µg)	53 (28)	42 (19)
Propacetamol (%)	47 {90}	21 {100}
Ketoprofen (%)	15 {29}	3 {14}
Delay between extubation and titration (min)	66 (36)	61 (37)
Body temperature (°C)	36.2 (2 5)	35.8 (0 8)
Total morphine dose (mg)	14 (8)	14 (8)
VAS at titration onset	78 (17)	64 (16)*

Patients' characteristics, surgical data, onset time of morphine titration, and total administered dose of morphine, are shown in Table 1. There were significantly more men and the surgical duration was shorter in the Awake group compared with the Sleep group. In the Sleep group, the mean time to the sleep onset of initiation of morphine titration was 22 (10) min.

Values of RS were comparable with Tonset in both groups. The changes in RS were statistically different in the Sleep group compared with the Awake group. The RS increased in the Sleep group from 1.8 (0.4) at STonset to 3.2 (0.6) at ST2 then remained stable afterwards until ST4. Conversely, the RS remained unaltered throughout the whole study period (1.9 (0.3) at ATonset, 2.0 (0.4) at AT2, and 2.0 (0.4) at AT4) in the Awake group (*P*<0.05 *vs* Sleep group). Similarly, BIS was comparable at Tonset in both groups. Then, BIS dropped in the Sleep group (Fig. 1), whereas it remained stable throughout the study period in the Awake group (*P*<0.05 *vs* Sleep group).

The time-course of VAS for pain was comparable in the Sleep and Awake groups (Fig. 1). Nevertheless, at STsleep, VAS was still 47 (19) mm in the Sleep group. Even though mean VAS at ST4 was 39 (21) in the Sleep group, 13 patients in this group (25%) still had a VAS above 50 mm, 14 patients (27%) a VAS of 30–49 mm and 25 patients only (48%) had a VAS below 30 mm (Fig. 2A). Individual analysis revealed that the patients who maintained a VAS above 50 mm after Tonset were the same at ST2, ST3, and ST4. However, the same analysis by sub-groups of VAS (below 30 mm, between 30 and 49, and above 50 mm) performed at AT2, AT3, and AT4 in the Awake group showed a constant and regular decrease of VAS over time (Fig. 2B).

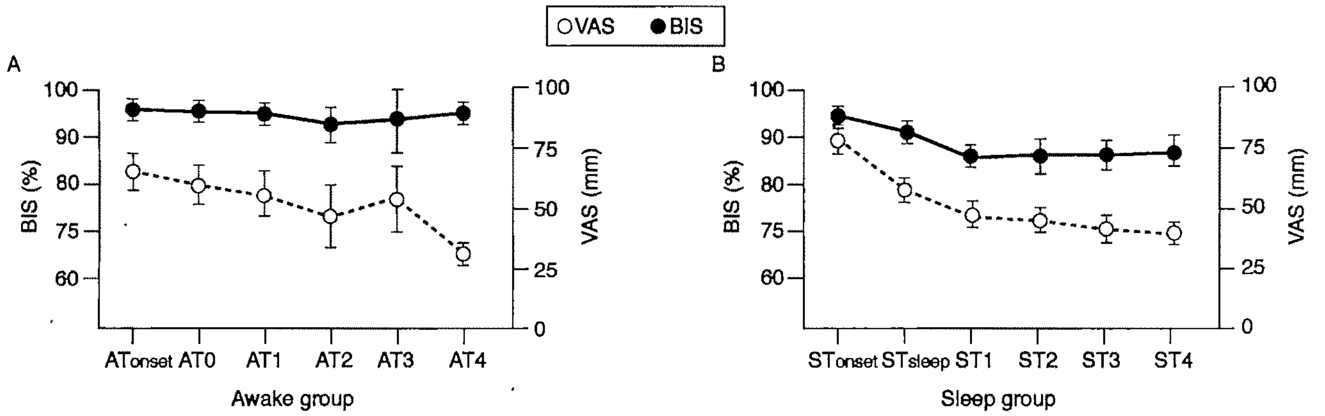


Fig 1 Evolution of the BIS and of VAS in the Sleep and Awake groups. Values are mean (SD) In the Sleep group, BIS and VAS were assessed just before the onset of titration (STonset), when patients started to sleep (STsleep), then 5 (ST1), 10 (ST2), 20 (ST3), and 30 min (ST4) after the onset of sleep. In the Awake group, BIS and VAS were recorded just before the onset of titration (ATonset), then at 5 (ATO), 10 (AT1), 20 (AT2), 30 min (AT3), and at the end of titration (AT4) (A) BIS and VAS evolution in the Awake group: BIS value remained stable over the entire study period and VAS decreased regularly over time. (B) BIS and VAS evolution in the Sleep group: BIS decreased from 95 (5) at STonset to 90 (10) at STsleep then remained on a plateau until ST4 (*P*<0.05 *vs* Sleep group) The time-course of VAS was comparable with the evolution of VAS observed in the Awake group.

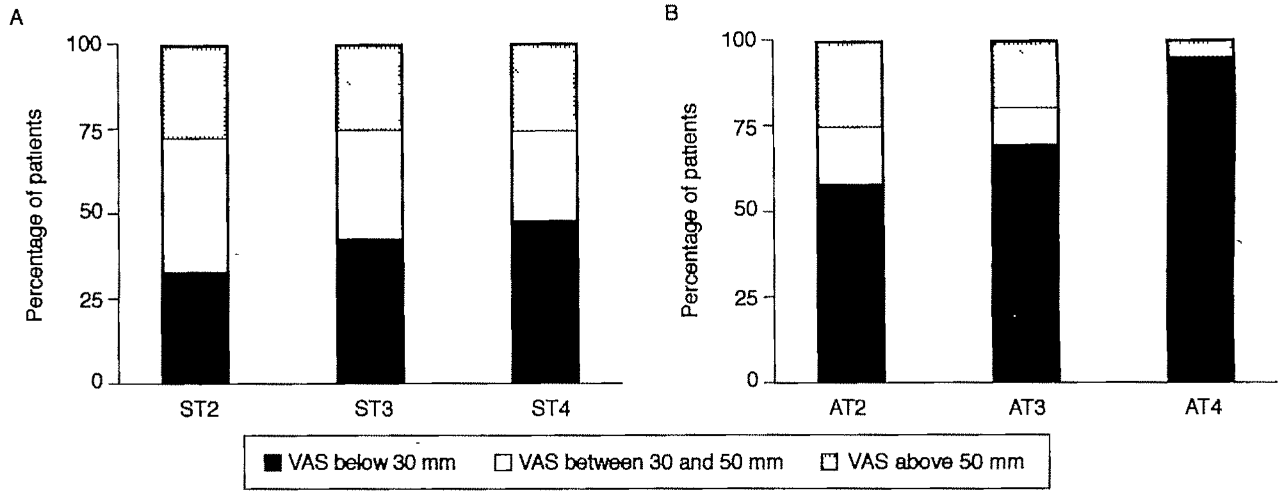


Fig 2 Division into subgroups, according to VAS Values are percentages Patients in the Sleep group were separated into three subgroups according to their VAS, 10 (ST2), 20 (ST3) and 30 (ST4) min after onset of sleep. Similarly, the same analysis by subgroup was performed among the patients of the Awake group 20 (AT2) and 30 (AT3) min after the onset of morphine titration as well as at the end of titration (AT4). In the Sleep group (A), analgesia progressively improved over time in 25% of patients Then, at ST4, VAS was below 30 mm in 48% of patients. Conversely, 25% of patients in Sleep group had a persistent high level of VAS, not decreasing over time. In the Awake group (B), a constant decrease in the percentage of patients with a VAS above 30 mm was observed over time. In the Awake group at AT4, VAS was below 30 mm in 95% of the patients

The VF did not change significantly over the study period (15 (4) *vs* 14 (4), *P* ns) and no significant intergroup difference occurred. Similarly, the Sp_{O_2} did not change significantly, nor was Sp_{O_2} significantly different between the Sleep and Awake groups (99 (2) *vs* 99 (2), *P* ns, respectively). The EMG significantly decreased over time between STonset/ATonset and ST4/AT4 in both groups (from 56 (13) to 43 (10) in Sleep group, $P<0.05$ ST4 *vs* STonset; from 51 (8) to 46 (7), $P<0.05$ AT4 *vs* ATonset), but no significant intergroup difference was found.

Discussion

The current study suggests that sedation during morphine titration occurs before patients have been completely relieved from their pain (as mean VAS at sleep onset was ~50 mm), and that sleep encountered during morphine titration is mainly related to the sedative properties of morphine. The second important finding of this study is that among patients in whom morphine titration is discontinued because of sedation, 25% still bear a high level of pain (VAS >50 mm) whereas only 50% have satisfactory pain relief (VAS <30 mm).

Sedation during i.v. morphine titration occurs in up to 60% of patients in PACU.[3] This sedation is often arbitrarily attributed to the occurrence of an adequate level of analgesia, for the patient who sleeps does not spontaneously express any pain. Nevertheless, the meaning of this sedation is not obvious, as many causes of sedation, such as an incomplete elimination of general anaesthetics and/or intra-operative opioids, exist in the PACU that might interfere with or potentiate the effects of i.v. morphine titration. In our study, this factor is unlikely to be important for there was a long delay between tracheal extubation and the onset of morphine titration (~1 h in both groups). Nevertheless, the duration of surgery in the Sleep group was greater than in the Awake group and a larger dose of sufentanil was given and presumably a larger dose of isoflurane. Therefore, the patients who had a longer anaesthetic might be more likely to fall asleep when given the same dose of morphine as those receiving a shorter anaesthetic. Finally, morphine itself might also induce deep sedation.[8 9] Therefore, occurrence of sedation during morphine titration does not necessarily imply that patients are relieved from their pain. In fact, the current study showed that at sleep onset during morphine titration, the VAS remained high (~50 mm).

The current study also identified three subgroups of patient among those who slept during titration: patients completely (VAS <30 mm), imperfectly (VAS between 30 and 50 mm) or not (VAS >50 mm) relieved at all from their pain, 30 min after morphine discontinuation. This last subgroup accounted for 25% of the patients who slept. An individual analysis (data not shown) showed that these were the same patients who had a VAS above 50 mm, 10, 20, and 30 min after the onset of sleep. Therefore, when a patient falls asleep while receiving morphine titration, failure of analgesia might probably be predicted early, when the VAS remains elevated 10 min after onset of sleep.

According to our local procedure, the PACU nurses discontinued i.v. morphine titration when the RS became greater than 2.[3] This cut-off value was arbitrarily chosen for safety reasons, in order to avoid very deep sedation and respiratory depression.[3] Nevertheless, neither respiratory depression as measured by Sp_{O_2} and ventilatory frequency, nor deep sedation (RS >4) was ever observed during the study period. Furthermore, in a previous study on 1200 patients, only one was given naloxone to reverse respiratory depression.[3] It is possible that a cut-off value of the RS at three instead of two might allow patients to receive a little more morphine providing a better pain relief with no or little increment of respiratory depression. At the present time, however, no study currently supports this hypothesis from a safety point of view.

Interference between electroencephalographic activity and EMG is probably a major pitfall during BIS monitoring and has been reported previously as providing a false elevation of BIS values in anaesthetized patients.[10] Also, BIS is usually artificially overestimated by the EMG activity in sedated and ventilated patients in the intensive care unit.[7] This overestimation is not predictable and might therefore represent a possible bias in the interpretation of the BIS value in awake patients. As EMG activity is generally elevated in awake patients in PACU, the Awake group was designed as a control group in whom patients remained not sedated during morphine titration. Therefore, we could compare the changes in EMG in both the Sleep and Awake groups and then assess the influence of EMG on the BIS recording in these two groups. We did not find any significant difference in EMG between the groups. The results from the current study confirm that alteration in the EMG activity does not account for the decrease in the BIS observed in the Sleep group. The current study suggests that BIS monitoring might represent an interesting alternative to the RS in the assessment of depth of sedation in the PACU. The main value of the BIS over the RS is that it provides a continuous assessment of the sedation level.

Nevertheless, factors other than EMG activity limit the interpretation of the BIS in the intensive care unit and PACU. Hypothermia,[11] shivering, poor signal quality (quality index signal <50%), spontaneous patient movements inducing signal loss, electrical interference from the forced-air warming systems[12] or pacemakers[13] are possible causes of misinterpretation of the BIS signal. In the current study, temperature was monitored and patients had a mean temperature of 36.2 and 35.8°C in the Sleep and Awake groups, respectively, which is compatible with an accurate recording of the BIS.[14] We also considered possible electrical interference, and we particularly avoided the use of any forced-air warming blanket.

In conclusion, the current study provides new insights into the mechanisms of action of morphine during i.v. titration for acute postoperative pain in PACU. First, we showed that when patients sleep during morphine titration, sedation and analgesia have a different time-course, sedation occurring before analgesia. Secondly, only 48% of patients who sleep during morphine titration are relieved from their pain, 27% still express moderate pain (VAS between 30 and 50 mm). The remaining 25% of patients still endure high pain scores (VAS >50 mm) 30 min after the discontinuation of morphine titration. Finally, this study suggests that morphine-induced sedation should not be considered as an indirect indicator of a correct level of analgesia during i.v. morphine titration.

Acknowledgement

We thank Dr David Baker MD, FRCA, of the Department of Anaesthesiology and Critical Care, CHU Necker-Enfants Malades, Paris, France, for reviewing the manuscript.

References

1 Edward WT, Breed RJ. The treatment of acute postoperative pain in postanesthesia care unit. *Anesthesiol Clin* 1990; **8**: 235–65

2 Owen H, Mather LE, Runciman WB, Carapetis RJ, Upton RN. The lockout interval in patient-controlled analgesia: a rationale basis for choice? *Br J Anaesth* 1987; **59**: 1328–9

3 Aubrun F, Monsel S, Langeron S, Coriat P, Riou B Postoperative titration of intravenous morphine. *Eur J Anaesthesiol* 2001; **18**. 159–65

4 Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. *Br Med J* 1974; **2**. 656–9

5 Gan TJ, Glass PS, Windsor A, *et al.* Bispectral index monitoring allows faster emergence and improved recovery from propofol, alfentanil, and nitrous oxide anesthesia. *Anesthesiology* 1997; **87**: 808–15

6 Simmons LE, Riker RR, Prato BS, Fraser GL. Assessing sedation during intensive care unit mechanical ventilation with the Bispectral Index and the Sedation-Agitation Scale. *Crit Care Med* 1999; **27**: 1499–1504

7 De Deyne C, Struys M, Decruyenaere J, *et al.* Use of continuous bispectral EEG monitoring to assess depth of sedation in ICU patients. *Intensive Care Med* 1998; **24**: 1294–8

8 Arunasalam K, Davenport HT, Painter S, Jones JG. Ventilatory response to morphine in young and old subjects. *Anaesthesia* 1983; **38**: 529–33

9 Catley DM, Thornton C, Jordan B, et *al.* Pronounced episodic oxygen desaturation in the postoperative period: its association with ventilatory pattern and analgesic regimen. *Anesthesiology* 1985; **63**: 20–28

10 Bruhn J, Bouillon TW, Shafer SL. Electromyographic activity falsely elevates the bispectral index. *Anesthesiology* 2000; **92**: 1485–7

11 Mychaskiw G, Heath BJ, Eichhorn JH. Falsely elevated bispectral index during deep hypothermic circulatory arrest. *Br J Anaesth* 2000; **85**: 798–800

12 Guignard B, Chauvin M. Bispectral index increases and decreases are not always signs of inadequate anesthesia. *Anesthesiology* 2000; **92**: 903

13 Gallagher JD. Pacer-induced artifact in the bispectral index during cardiac surgery. *Anesthesiology* 1999, **90**: 636

14 Lopez M, Ozaki M, Sessler DI, Valdes M. Mild core hyperthermia does not alter electroencephalographic responses during epidural-enflurane anesthesia in humans. *J Clin Anesth* 1993; **5**· 425–30

British Journal of Anaesthesia **89** (5): 702–6 (2002)

Spinal anaesthesia: comparison of plain ropivacaine 5 mg ml^{-1} with bupivacaine 5 mg ml^{-1} for major orthopaedic surgery

D. A. McNamee[1]*, A. M. McClelland[1], S. Scott[1], K. R. Milligan[2], L. Westman[3] and U. Gustafsson[3]

[1]Department of Anaesthetics and Intensive Care Medicine, The Queen's University of Belfast, Whitla Medical Building, 97 Lisburn Road, Belfast BT9 7BL, UK. [2]Department of Anaesthetics, Musgrave Park Hospital, Stockmans Lane, Belfast, UK. [3]AstraZeneca R&D, Sodertalje, Sweden

**Corresponding author*

Background. Ropivacaine provides effective spinal anaesthesia for total hip arthroplasty. This study was designed to compare the efficacy and safety of plain ropivacaine with plain bupivacaine for spinal anaesthesia in patients undergoing total hip arthroplasty.

Methods. Sixty-six patients, ASA I or II, were randomized to receive an intrathecal injection of one of two local anaesthetic solutions. Group R (n=32) received 3.5 ml of ropivacaine 5 mg ml^{-1} (17.5 mg). Group B (n=34) received 3.5 ml of bupivacaine 5 mg ml^{-1} (17.5 mg). The onset and duration of sensory block at dermatome level T10, maximum upper and lower spread of sensory block and the onset, intensity and duration of motor block were recorded, as were safety data.

Results. Onset of motor and sensory block was rapid with no significant differences between the two groups. The median time of onset of sensory block at the T10 dermatome was 2 min (range 2–5 min) in Group R and 2 min in Group B (range 2–9 min). The median duration of sensory block at the T10 dermatome was 3.0 h (range 1.5–4.6 h) in Group R and 3.5 h (2.7–5.2 h) in Group B (P<0.0001). The median duration of complete motor block (modified Bromage Scale 3) was significantly shorter in the ropivacaine group compared with the bupivacaine group (2.1 vs 3.9 h, P<0.001).

Conclusions. Intrathecal administration of either 17.5 mg plain ropivacaine or 17.5 mg plain bupivacaine was well tolerated and an adequate block for total hip arthroplasty was achieved in all patients. A more rapid postoperative recovery of sensory and motor function was seen in Group R compared with Group B.

Br J Anaesth 2002; **89**: 702–6

Keywords: anaesthetic techniques, regional; anaesthetic techniques, subarachnoid; anaesthetics, local, ropivacaine; anaesthetics local, bupivacaine; surgery, total hip replacement

Accepted for publication: May 30, 2002

Ropivacaine is an amide local anaesthetic with local anaesthetic properties similar to those of bupivacaine.[1 2] It is presented as a single-enantiomer and has been used extensively for local infiltration, epidural, and peripheral nerve block. Extensive clinical data have shown that ropivacaine is effective and safe for regional anaesthetic techniques such as epidural and brachial plexus block.[3] However, experience of intrathecal anaesthesia with ropivacaine is not as well documented.

In a previous study we have demonstrated that intrathecal administration of ropivacaine (plain 18.75 and 25 mg) is well tolerated and provides effective anaesthesia for total hip arthroplasty surgery.[4] To our knowledge, no studies have compared intrathecal ropivacaine with bupivacaine, the standard agent, in patients undergoing major surgery. This study was designed to compare the safety and efficacy of intrathecal plain ropivacaine 17.5 mg (baricity 0.9988 at 37°C) and plain bupivacaine 17.5 mg (baricity 0.9988 at 37°C) in patients undergoing primary total hip arthroplasty.

Methods

A Clinical Trials Exemption Certificate was obtained from the Medicines Control Agency and approval for this

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Table 1 Patient characteristics and duration of surgery (median (range))

	Ropivacaine 17.5 mg	**Bupivacaine 17.5 mg**
Age (yr)	66 (33–78)	67 (34–77)
Height (cm)	170 (161–189)	168 (160–184)
Weight (kg)	79 (64–97)	80 (60–106)
Gender (M/F)	21/11	22/12
ASA I/II/III	8/24/0	12/22/0
Duration of surgery (h)	1.0 (0.7–2.6)	0.9 (0.7–2.1)

randomized, double-blind study was granted by the Research Ethics Committee of the Queen's University of Belfast. Written informed consent was obtained from 66 patients who fulfilled the following inclusion criteria: undergoing primary unilateral total hip arthroplasty (cemented prosthesis) under intrathecal anaesthesia, ASA I–III, age 18–80 yr, height ⩾160 cm, and weight 60–110 kg. Patients who had contraindications to spinal anaesthesia, allergy to amide local anaesthetics, a significant history of substance abuse, who had participated in clinical trials in the preceding 3 months, had been enrolled previously in this study or had significant derangement of laboratory values and women of child bearing potential were excluded.

Oral premedication consisted of diazepam 10 mg and ranitidine 150 mg. Following arrival in the anaesthetic room, i.v. access was established, full non-invasive monitoring applied and the patient placed in the lateral position with the affected hip uppermost. Following skin infiltration with 1% lidocaine a 20 G introducer needle was inserted at the L2/3 or the L3/4 interspace through which a 25 G pencil point needle with its opening uppermost was passed. Correct needle placement was identified by free flow of cerebrospinal fluid and 3.5 ml (17.5 mg) study drug was injected over 10 s. Group R received plain 0.5% ropivacaine, Group B received plain 0.5% bupivacaine. The local anaesthetic solutions were presented in identical numbered ampoules to ensure blinding. The spinal needle was removed and the patient placed supine to carry out the initial assessments. Following completion of these and before the commencement of surgery, patients were returned to the lateral position and a continuous i.v. infusion of 1% propofol started. The rate of this infusion was adjusted to render the patients drowsy but rousable. Surgery was commenced within 45 min of the administration of the study drug.

The upper and lower spread of sensory block was determined bilaterally using loss of sensation to ice. The dermatomes were identified by reference to a standard diagram. Sensory block was assessed at 2 and 5 min post-injection and at 5-min intervals thereafter until two consecutive levels of sensory block were identical. Assessments were continued at 30-min intervals following the completion of surgery until normal sensation returned. The degree of motor block in the non-operative leg was assessed at the same time points as sensory block using a modified Bromage scale (0=no motor block, 1=inability to raise extended legs, 2=inability to flex knees, and 3=inability to flex ankle joints). Assessment of motor block ceased once normal motor function returned. Heart rate and arterial pressure were recorded using standard non-invasive monitors before intrathecal injection and thereafter at 5, 10, 15, 20, 25, 30, 45, and 60 min, then hourly until 8 h post-injection.

The time to first request for postoperative analgesia and the total morphine consumption in the first 24 h following surgery were noted, as well as intraoperative blood loss. The quality of anaesthesia as judged by the anaesthetist, the quality of muscle relaxation as judged by the surgeon, the degree of intraoperative comfort as judged by the patient were recorded as excellent, satisfactory, or unsatisfactory. Patients were followed up daily for adverse events for the duration of their hospital stay and again by telephone 14–21 days post-surgery.

A difference of 60 min in the duration of motor block (modified Bromage score ⩾1) was taken to be clinically significant. An estimated 26 patients per group were necessary to detect a 60-min difference in the duration of motor block with an 80% power, based on a simple unstratified two-sample 95% *t*-based confidence interval for group comparison. The Stratified Wilcoxon (mid) rank sum test was used for comparison between the two groups. A P value of <0.05 was considered statistically significant.

Results

The characteristics of the two groups were comparable in terms of age, height, weight, gender, and ASA classification. There was no significant difference in the duration of surgery (see Table 1). Sixty-eight patients were randomized to the two treatment groups. Two of these patients were excluded from the study, both from the ropivacaine 5 mg ml^{-1} group: one due to withdrawal of consent before arrival in the anaesthetic room, the other due to spillage of the study drug before commencement of intrathecal injection. All patients were able to co-operate fully with the subsequent assessments.

There was no significant difference in the median time of onset of sensory block at the T10 dermatome, which was 2 min (range 2–5 min) in the ropivacaine group and 2 min (range 2–9 min) in the bupivacaine group. The median duration of sensory block at the T10 dermatome was significantly longer in the bupivacaine group: 3.5 h (range 2.7–5.2 h) compared with 3.0 h (range 1.5–4.6 h) in the ropivacaine group (P<0.0001).

There was a trend for patients in the bupivacaine group to achieve a higher upper dermatome level of sensory block but this difference was not significant (Fig. 1). The lower distribution of spread of sensory block was similar in both groups.

Whilst there was an overall trend towards a longer duration of sensory block at dermatome levels other than T10 in the bupivacaine group, this difference was not

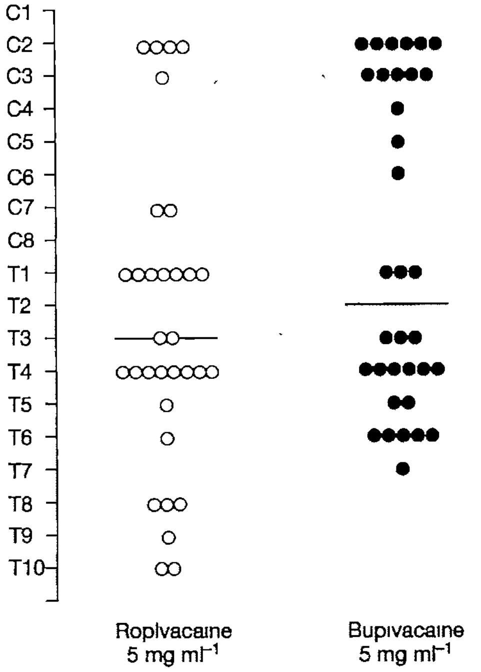


Fig 1 Upper extent of levels of analgesia in the individual patients after intrathecal administration of isobaric ropivacaine 5 mg ml^{-1} or bupivacaine 5 mg ml^{-1}. Horizontal bars represent medians. No significant differences

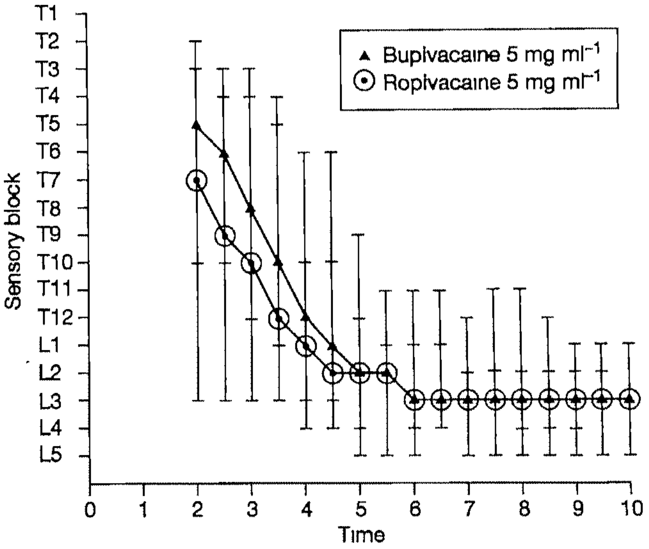


Fig 2 Regression of upper dermatomal level of sensory block with time (median and range) after intrathecal administration of isobaric ropivacaine 5 mg ml^{-1} or bupivacaine 5 mg ml^{-1}. Median duration of sensory block at the T10 dermatome was significantly longer in the bupivacaine group ($P<0.0001$).

statistically significant. The duration of sensory block in each group is shown in Figure 2.

The onset of motor block was rapid in both groups with a median onset time of 2 min to achieve a Bromage score of 1 for both groups and a median onset time of 4 min to achieve a Bromage score of 2 for both groups. All patients in the bupivacaine group and all but one in the ropivacaine group achieved Bromage of at least 1. Onset of motor block was prolonged in some patients in both groups who failed to report any degree of motor block until after surgery. As no assessments were carried out during surgery, this delay was probably exaggerated.

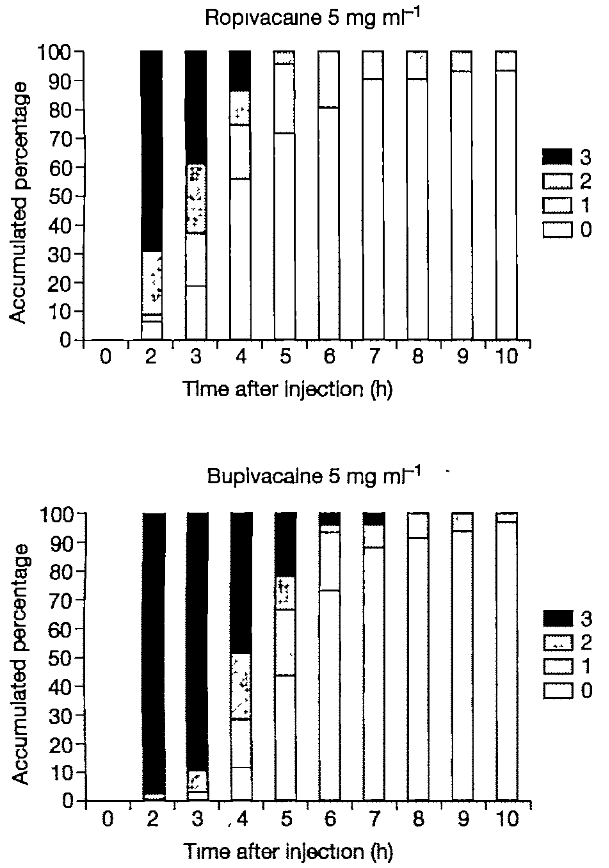
The median time of onset to achieve a Bromage score of 3 was 10 min in the ropivacaine group and 8 min in the bupivacaine group. This difference was not significant. The median duration of complete motor block (modified Bromage Scale 3) was significantly shorter in the ropivacaine group compared with the bupivacaine group (2.1 *vs* 3.9 h, $P<0.001$). After surgery, the degree of motor block was lower in the ropivacaine patients compared with patients receiving bupivacaine (Fig. 3). At 2 h after intrathecal injection, 69% of the patients in the ropivacaine group, and 97% of the patients in the bupivacaine group, had a Bromage score of 3. At 4 h after injection 56% of the ropivacaine patients had no detectable motor block (Bromage score 0), whereas the corresponding figure in the bupivacaine patients was 12%.

Anaesthesia was judged to be excellent in all patients, except for one patient in the ropivacaine group in whom it was judged to be satisfactory. No patients required supplemental analgesia intraoperatively. Excellent muscle relaxation was reported in all but one patient in each group. The median time to first analgesic request was significantly shorter in the ropivacaine group than in the bupivacaine group (3.4 *vs* 4.9 h, $P<0.001$). There was a trend towards higher morphine requirements in the ropivacaine group (median 54 mg, range 12–86 mg) than in the bupivacaine group (median 44 mg, range 7–99 mg) although this difference was not statistically significant.

Both intrathecal ropivacaine and bupivacaine produced an initial moderate fall in arterial pressure in keeping with the expected sympathetic block produced by spinal anaesthesia. Intraoperative hypotension requiring treatment with i.v. ephedrine occurred in 12% of patients in ropivacaine groups (range 5–35 mg) and in 26% of patients in the bupivacaine group (range 5–35 mg). Two patients in the ropivacaine group also required atropine 0.6 mg for the treatment of bradycardia compared with none in the bupivacaine group. The most commonly reported adverse events during the first 24 h were oliguria, nausea, pyrexia, hypotension, and vomiting. These events were equally distributed between groups. There was no difference in the blood loss between the two groups (median blood loss was 350 ml for both groups).

Discussion

This study shows that intrathecal administration of either 17.5 mg ropivacaine or 17.5 mg bupivacaine was well


Ropivacaine 5 mg ml^{-1}

Bupivacaine 5 mg ml^{-1}

Fig 3 Motor block following intrathecal administration of isobaric ropivacaine 5 mg ml^{-1} or bupivacaine 5 mg ml^{-1} Numbers represent modified Bromage Scale. Median duration of complete motor block (modified Bromage Scale 3) significantly shorter in the ropivacaine group ($P<0.001$).

tolerated and an adequate block for total hip arthroplasty was achieved in all patients.

Intrathecal ropivacaine does not produce any signs of neurotoxicity following administration to rats.[5,6] In dogs intrathecal ropivacaine has been shown to produce effective local anaesthesia with an equipotent sensory block but shorter duration of motor block than intrathecal bupivacaine.[7] In humans, ropivacaine has been shown to be effective in providing intrathecal anaesthesia for patients undergoing total hip replacement,[4] transurethral resection of the prostate,[8] and lower abdominal or limb surgery.[9,10] The present study is the first, to our knowledge, to compare intrathecal ropivacaine with bupivacaine as a sole anaesthetic agent in patients undergoing major orthopaedic surgery. The efficacy and safety of two glucose-free solutions, ropivacaine 5 mg ml^{-1} and bupivacaine 5 mg ml^{-1}, were assessed.

In the present study, both solutions produced similar results in terms of onset and spread of analgesia. Both the ropivacaine and bupivacaine solutions exhibited variation in the degree of spread of sensory block, which may be attributed to the use of a plain solution.

Gautier and colleagues[11] compared 4 ml of intrathecal hyperbaric 0.2% bupivacaine (8 mg) with 4 ml of 0.2, 0.25, 0.3, or 0.35% hyperbaric ropivacaine (8, 10, 12, or 14 mg) in patients undergoing knee arthroscopy. They estimated that the 12 mg dose of ropivacaine was approximately equivalent to bupivacaine 8 mg. Although the duration of both sensory and motor block was significantly shorter in the ropivacaine group in our study, these differences were not as pronounced as those seen in the above-mentioned study. This may reflect a difference in the dosage use, the baricity of the solution used, the patient position and the population studied. Whiteside and others[10] compared equal doses (15 mg) of intrathecal 0.5% ropivacaine in 10 mg ml^{-1} or 50 mg ml^{-1} glucose in two groups of patients undergoing a variety of minor surgical procedures. They showed that the onset of sensory block to T10 was significantly faster in the glucose 50 mg ml^{-1} group but that maximum extent of sensory block, time to block regression and quality and duration of motor block were similar in both groups. In keeping with our findings, all patients demonstrated sensory block adequate for surgery.

In another recent study, in patients undergoing transurethral resection of the bladder or prostate, patients were randomized to receive either 5 ml of 0.2% isobaric bupivacaine (10 mg) or 5 ml 0.3% isobaric ropivacaine (15 mg) for spinal anaesthesia.[8] Despite the fact that a lower dose of bupivacaine was used in comparison with ropivacaine, there was a significant increase in the cephalad spread of the sensory block in the bupivacaine group. The degree of motor block was similar which is in accordance with our study, where a lower intensity of motor block was seen with ropivacaine than with bupivacaine with the same dose.

Polley and colleagues[12] investigated the minimum concentration of a fixed volume of an epidurally administered local anaesthetic required to abolish the pain of the first stage of labour. They ascertained that ropivacaine is approximately 40% less potent than bupivacaine in this situation. However other investigators have failed to demonstrate any differences between these two agents for epidural analgesia in labour.[13] Whilst there has been no evaluation of the differences in potency of these two agents following intrathecal administration, the difference in the duration of motor and sensory block seen in our study may be due to differences in potency. However these differences were not of the same order as those detected by Polley and co-workers.[12]

Twenty-two per cent of patients in the ropivacaine group and 41% of patients in the bupivacaine group had sensory anaesthesia in the cervical dermatomes. This is higher than recorded in studies using similar doses of ropivacaine carried out by van Kleef and colleagues[9] and by Malinovsky and co-workers,[8] but is similar to work carried out by McNamee and colleagues.[4] This may be due to a difference in the characteristics of the populations studied, or a difference in the position of the patient during the institution of intrathecal anaesthesia. Sensory block in our study was tested using loss of sensation to ice rather than loss of sensation to pin-prick as used by others.[9] This difference in the method of assessment of sensory block readily accounts for the discrepancy between the degree of sensory block achieved in these two studies.[14] The subgroup of patients with sensory anaesthesia in the cervical dermatomes did not demonstrate any upper limb motor weakness, respiratory distress, decrease in oxygen saturation, or cardiovascular compromise. This suggests a significant separation in the extent of motor and sensory block when loss of sensation to ice is used. Cervical sensory block to ice was not associated with any clinically significant adverse events. Although the upper extent of loss of sensation to ice only reached the T10 dermatome in two patients in the ropivacaine group this was not associated with any discomfort during or immediately following surgery.

Although previous studies have linked intrathecal ropivacaine with an increased incidence of post-dural puncture headache[9] and low back pain,[15] no patient in the present study reported symptoms in keeping with these two complications. This is in agreement with the findings of others.[4 8 11] The headache reported in the study by van Kleef and colleagues[9] is probably due to the fact that a Quinke type of spinal needle was used, compared with a Whitacre-needle in the present study. Furthermore, hip replacement is commonly performed in elderly patients in whom post-dural puncture headache is rare.

In terms of safety, both intrathecal ropivacaine and bupivacaine provided a high degree of cardiovascular stability with a low incidence of bradycardia. The degree of hypotension was felt to be predictable in an elderly population undergoing an operative procedure under a combination of spinal anaesthesia and propofol sedation. The hypotension seen was associated with the commencement of the i.v. infusion of 1% propofol rather than the institution of spinal anaesthesia.[16] The most commonly reported adverse events, oliguria, pyrexia, hypotension, nausea, and vomiting, were those commonly seen in connection with this type of surgery and there were no reports of postoperative neurological problems. Postoperative fever is commonly seen following total hip arthroplasty, and bone cement may also cause fever.[17] No serious problems were associated with these adverse effects and they were treated according to hospital routine.

In conclusion, intrathecal administration of either 17.5 mg ropivacaine or 17.5 mg bupivacaine was well-tolerated and provided similar, effective anaesthesia for total hip arthroplasty. In an equal milligram dose, bupivacaine produced a more prolonged sensory and motor block. Intrathecal ropivacaine may prove useful when surgical anaesthesia of a similar quality but of a shorter duration than that of bupivacaine is desired. Thus, ropivacaine offers a reliable motor block for major orthopaedic surgery, with a predictable and rapid return of motor function after surgery.

Acknowledgements

We would like to thank Mr D. Beverland and the other consultant orthopaedic surgeons for their patience and assistance with the scheduling of suitable cases and the nursing staff of Musgrave Park Hospital for their help in carrying out the observations This research was supported by a grant from AstraZeneca Pharmaceuticals Ltd

References

1 Akerman B, Hellberg B, Trossvik C. Primary evaluation of the local anaesthetic properties of the amino amide agent ropivacaine (LEA 103). *Acta Anaesthesiol Scand* 1988; **32**: 571–8

2 McClure JH. Ropivacaine. *Br J Anaesth* 1996; **76**: 300–7

3 McClellan KJ, Faulds D. Ropivacaine—an update of its use in regional anesthesia. *Drugs* 2000; **60**: 1065–93

4 McNamee DA, Parks L, McClelland AM, *et al.* Intrathecal ropivacaine for total hip arthroplasty: double-blind comparative study with isobaric 7.5 mg ml^{-1} and 10 mg ml^{-1} solutions. *Br J Anaesth* 2001; **87**: 743–7

5 Kristensen JD, Karlsten R, Gordh T. Spinal cord blood flow after intrathecal injection of ropivacaine and bupivacaine with or without epinephrine in rats. *Acta Anaesthesiol Scand* 1998; **42**: 685–90

6 Kristensen JD, Karlsten R, Gordh T. Spinal cord blood flow after intrathecal injection of ropivacaine: a screening for neurotoxic effects. *Anesth Analg* 1996; **82**: 636–40

7 Feldman HS, Covino BG. Comparative motor-blocking effects of bupivacaine and ropivacaine, a new amino amide local anesthetic, in the rat and dog. *Anesth Analg* 1988; **67**: 1047–52

8 Malinovsky JM, Charles F, Kick O, *et al.* Intrathecal anesthesia: ropivacaine versus bupivacaine. *Anesth Analg* 2000, **91**: 1457–60

9 vanKleef JW, Veering BT, Burm AGL. Spinal anesthesia with ropivacaine: a double-blind study of efficacy and safety of 0.5% and 0.75% solutions in patients undergoing minor lower limb surgery. *Anesth Analg* 1994; **78**: 1125–30

10 Whiteside JB, Burke D, Wildsmith JAW. Spinal anaesthesia with ropivacine 5 mg ml^{-1} in glucose 10 mg ml^{-1} and 50 mg ml^{-1}. *Br J Anaesth* 2001; **86**: 241–4

11 Gautier PE, De Kock M, Van Steenberge A, *et al.* Intrathecal ropivacaine for ambulatory surgery. A comparison between intrathecal bupivacaine and intrathecal ropivacaine for knee arthroscopy. *Anesthesiology* 1999; **91**: 1239–45

12 Polley LS, Columb MO, Naughton NN, Wagner DS, van de Ven CJM. Relative analgesic potencies of ropivacaine and bupivacaine for epidural analgesia in labour. *Anesthesiology* 1999; **90**: 944–50

13 Stienstra R, Jonker JA, Bourdrez P, Kuijpers JC, van Kleef JW, Lundberg U. Ropivacaine 0.25% versus bupivacaine 0.25% for continuous epidural analgesia in labour: a double blind comparison. *Anesth Analg* 1995; **80**: 285–9

14 Liu SS, Ware PD. Differential sensory block after spinal bupivacaine in volunteers. *Anesth Analg* 1997; **84**: 115–19

15 McDonald SB, Liu SS, Kopacz DJ, Stephenson CA. Hyperbaric spinal ropivacaine. A comparison to bupivacaine in volunteers. *Anesthesiology* 1999; **90**: 971–7

16 Muzi M, Berens RA, Kampine JP, Ebert TJ. Venodilation contributes to propofol-mediated hypotension in humans. *Anesth Analg* 1992; **74**: 877–83

17 Kirwan WO. Systemic phenomena and bone cement. *Irish J Med Sci* 1973; **142**: 342–5

British Journal of Anaesthesia 89 (5): 707–10 (2002)

Paediatric regional anaesthesia, a survey of practice in the United Kingdom

J. C. Sanders*

Hope Hospital, Stott Lane, Salford, UK

**Present address and address for correspondence: Department of Anesthesiology and Critical Care Medicine, University of New Mexico Health Sciences Center, Surge Building, 2701 Frontier NE, Albuquerque, NM 87131–5216, USA*

Background. A variety of techniques and drugs, many unlicensed, is used in paediatric regional anaesthesia. This study is the first to survey paediatric anaesthetists about the techniques and drugs used in paediatric regional anaesthesia. The aim is to provide a record and benchmark of UK practice.

Methods. A postal questionnaire was sent to all members of the Association of Paediatric Anaesthetists residing in the UK. Information was requested on the type of hospital worked in, years of practice, paediatric anaesthesia workload, regional anaesthesia techniques used, and drugs used in regional anaesthesia.

Results. A total of 220 responses from 264 questionnaires (83.3%) were received. Of these respondents, 155 (70%) practised paediatric anaesthesia as more than 50% of their workload, and 10 had retired or returned blank forms. Two hundred and two of 210 (96%) use caudal anaesthesia and 151 (72%) use caudal, epidural and peripheral block. One hundred and ninety-two of 210 (91%) have no lower age limit for using caudal anaesthesia. One hundred and twenty-three of 210 anaesthetists (58%) used adjuvants with local anaesthetics in caudal block, the most common being fentanyl [44/210 (21%)], clonidine [55/210 (26%)], diamorphine [27/210 (13%)] and ketamine [67/210 (32%)]. Those working in specialist centres or teaching hospitals or who had a greater paediatric anaesthesia workload were more likely to use a greater variety of regional anaesthesia techniques.

Conclusions. Caudal anaesthesia is widely used for patients of all ages by almost all practitioners. Most anaesthetists at all hospital types and experience levels use adjuvants with local anaesthetics when performing caudal anaesthesia. Those with more experience in paediatric anaesthesia and those in specialist centres commonly use other neuraxial and peripheral block techniques.

Br J Anaesth 2002; **89**: 707–10

Keywords: anaesthesia, paediatric; anaesthetic techniques, epidural; anaesthetic techniques, regional

Accepted for publication: July 9, 2002

Anecdotal evidence suggests that a large variety of techniques and drugs, including many unlicensed for this use, is commonly used in the practice of paediatric regional anaesthesia. Little is known about how consultant colleagues perform paediatric regional anaesthesia, especially outside of one's own institution. This study aimed to discover the patterns of usage of drugs and techniques in regional anaesthesia by paediatric anaesthetists in the UK in order to present the current state of practice.

Methods

After approval by the Audit Department, Royal Manchester Children's Hospital and the Secretary of the Association of

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Table 1 Drugs added to local anaesthetic solutions in paediatric caudal anaesthesia, frequency of usage and doses used

Drug added to local anaesthetic	Frequency of use by 210 respondents (%)	95% confidence intervals for percentage	Dose range (mode)
Epinephrine	24 (11)	7.5, 16.5	1:200,000
Fentanyl	44 (21)	15.7, 27.1	0.5–4.0 μg ml^{-1} (2.0 μg ml^{-1})
Diamorphine	27 (13)	8.7, 18.2	20–50 μg ml^{-1} (20 μg ml^{-1})
Clonidine	55 (26)	20.4, 32.7	0.5–2.5 μg ml^{-1} (2.0 μg ml^{-1})
Ketamine	67 (32)	25.7, 38.7	0.25–1.00 mg ml^{-1} (0.50 mg ml^{-1})
Bicarbonate	7 (3)	1.4, 6.8	Not specified
Morphine	4 (2)	0.5, 4.8	50–100 μg ml^{-1} (50 μg ml^{-1})
Midazolam	1 (0.5)	0, 2.6	0.5 μg ml^{-1}

Paediatric Anaesthetists, a postal questionnaire was sent to all members of the Association of Paediatric Anaesthetists residing in the UK. Information was sought on the type of hospital worked in, paediatric anaesthesia workload, years of practice as a consultant in paediatric anaesthesia, regional anaesthesia techniques used and drugs used in the practice of regional anaesthesia. Specific questions were asked about doses of drugs for which at least two articles describing their use in paediatric regional anaesthesia had been published in at least two major anaesthesia journals, based on a Medline search.

A follow-up questionnaire and covering letter were sent to non-respondents 1 month later. Data were coded anonymously and entered into a Microsoft Access database by the Audit Department, Royal Children's Hospital, Manchester. Those interpreting the data had no information on the identity of respondents. Statistical analysis was performed using SAS statistical programs and StatXact-4. Differences between groups were tested using Fisher's exact test. Trend analysis was done using the Jonckheere–Terpstra test; 95% confidence intervals are given in Table 1. $P<0.05$ was considered to be statistically significant.

Results

Replies were received to 220 of the 264 (83.3%) questionnaires sent. No bias was detected in the characteristics of the respondents. Ninety-seven of 220 (44%) had more than 90% of their workload in paediatric anaesthesia; 155 (70%) had more than 50% of their workload in paediatric anaesthesia. Ninety-three of 220 (42%) worked in a specialist paediatric centre, 79 (36%) worked in a teaching hospital, 10 (5%) worked in both a specialist paediatric centre and a teaching hospital, and 26 (12%) worked in a district general hospital. Two were solely private practitioners. Nine respondents had retired and one returned a blank questionnaire. These 10 responses were not considered in the analysis of clinical practice.

Eleven of 220 (5%) respondents practised paediatric anaesthesia for two or fewer sessions a week, 58 (26%) for 3–5 sessions a week and 141 (64%) for more than six sessions a week. One hundred and fourteen (52%) had practised in paediatric anaesthesia for fewer than 10 yr and 96 (44%) for 10 yr or more. The type of hospital worked in was significantly associated with the number of sessions devoted to paediatric anaesthesia and the percentage workload in paediatric anaesthesia (Jonckheere–Terpstra, $P<0.001$): specialist paediatric centre>teaching hospital>district general hospital.

Of 210 practising respondents, 202 (96%) used caudal anaesthesia, 151 (72%) used caudal, epidural and peripheral nerve block, 24 (11%) used only caudal and peripheral nerve block, 14 (7%) used only caudal and epidural block, 13 (6%) used caudal anaesthesia as their only regional technique, and 8 (4%) used no regional anaesthesia. Practitioners were more likely to use caudal, epidural and peripheral nerve block if a greater percentage of their workload was in paediatric anaesthesia (Fisher's exact test, $P<0.001$), if they had more than three paediatric anaesthesia sessions a week ($P=0.02$), or they worked in a teaching hospital or specialist paediatric centre ($P=0.002$). Practitioners who used only caudal anaesthesia and no other paediatric regional anaesthesia techniques were more likely to work in a district general hospital ($P<0.001$).

One hundred and ninety-two of 210 practising respondents (91%) considered there to be no minimum age of patient suitable for caudal anaesthesia. The ten anaesthetists who used a minimum-age cut-off stated it as being in the range from 40 weeks post-conception to 3 yr.

Of 210 practising respondents, 198 (94%) used bupivacaine as the local anaesthetic in caudal anaesthesia, and 28 (13%) used ropivacaine. Mixtures of local anaesthetics were used by 22 (10%). The use of adjuvant drugs for caudal anaesthesia is shown in Table 1. Eighty-seven respondents used additive drugs with local anaesthetics in peripheral nerve block: 59 (28%) used opioids and 30 (14%) used epinephrine.

A complete set of the data in SAS and Microsoft Excel format can be obtained from the author.

Discussion

Relationships between characteristics of respondents show predicted internal consistencies that help to validate the data. The number of sessions a week doing paediatric anaesthesia parallels the percentage workload in paediatric anaesthesia. Those working in specialist paediatric centres have a greater paediatric workload than those in teaching hospitals, who in turn have a higher workload than those in district general hospitals. The number of years of practice as a paediatric anaesthetist did not vary between groups.

Members of the Association of Paediatric Anaesthetists were chosen as the target of the survey. Although their practice might not represent the practice of all anaesthetists in the UK, as consultants in paediatric anaesthesia, it could reasonably be considered as representative of the practice and opinions of experts in paediatric anaesthesia in the UK. This special interest could explain the high response rate to the questionnaire: 220 of 264 (83.3%).

Caudal anaesthesia, used by 96% of respondents, is the most widely used of the regional anaesthesia techniques in children. It is a relatively easy and safe technique, with a rate of catastrophic complications of about 1:40 000[1] and an overall rate of complications of 1.5:1000.[2] There is an increased risk of complications, especially unrecognized intravascular and intraosseous injections, in children weighing less than 10 kg.[3] This explains the reluctance of some to use this technique in the very young, although this study shows that the majority (91%) of anaesthetists have no lower age limit for patients to receive caudal anaesthesia. This reflects previously described practice in which caudal blocks were the most common, accounting for nearly 60% of all regional blocks and were performed in all age groups.[2] Of the eight anaesthetists not using caudal anaesthesia, six were in subspecialties for which they considered it inappropriate (cardiac, burns and ambulatory), although the use of caudal anaesthesia in these subspecialties is well documented. No information was sought on whether the regional anaesthesia was used primarily for intraoperative or postoperative considerations. It is assumed that those who added adjuvants to their local anaesthetic solutions did so to alter the quality of or to prolong the analgesia, which would be useful in the postoperative phase.

Bupivacaine is the most commonly used local anaesthetic drug in paediatric regional anaesthesia. Its long action, availability and well-documented use out-weigh its toxic effects. Particular care must be taken in dosing and re-dosing infants.[4] Ropivacaine is also used commonly and its use may be growing in popularity. Ropivacaine has been shown to be as effective in paediatric caudal anaesthesia,[5] to have fewer side-effects,[5] and less cardiac[6] and central nervous system[7] toxicity than bupivacaine.

The drugs most commonly added to local anaesthetic solutions—opioids,[8] clonidine,[9] and ketamine,[10]—have all been shown to increase safely the duration and quality of analgesia when administered neuraxially with local anaesthetics. Few anaesthetists use morphine as an agent for caudal anaesthesia: 4 of 210 (2%), compared with 27 (13%) who use diamorphine and 44 (21%) who use fentanyl, even though far more literature exists discussing the use of morphine in paediatric regional anaesthesia, and its neuraxial mechanism is better understood. Lipophilic opioids such as diamorphine and fentanyl may have fewer side-effects for an equi-analgesic dose but still require postoperative respiratory monitoring. *S*(+)-ketamine has been used as a sole agent for caudal analgesia with good effect and minimal side-effects.[11]

One hundred and seventy-five of 210 (84%) of respondents use peripheral block and 59 (28%) added opioids to the local anaesthetic solution. No attempt was made in this survey to determine which peripheral blocks were used. Evidence for the use of adjuvants in peripheral local anaesthetic block is inconsistent and the topic is little studied in children. Combining opioids[12] or clonidine[13] and local anaesthetics for peripheral nerve blocks does not appear to be consistently effective. Opioids combined with local anaesthetics have proven to be of clinical benefit when used for infiltration[14] or intra-articular injection,[15] where they can act on the peripheral opioid receptors, which are primarily found at the distal terminals of afferent fibres. Clonidine, in addition to its primary site of action as an agonist at central alpha-2 adrenoceptors, may also enhance peripheral block by a direct depressant effect on A- and C-fibre conduction.

There is a large similarity in the techniques and drugs used, although environment influences the types of regional anaesthesia blocks used. Those who have a greater part of their practice in paediatric anaesthesia or who work in specialist paediatric centres or teaching hospitals are more likely to perform a greater variety of blocks. This may be because they have more opportunity to develop a large repertoire of techniques or because they work in an environment more conducive to expanding their technical practice. Having more experienced colleagues and perioperative support could provide the confidence needed to use a wide range of techniques. Interestingly, the use of drugs and adjuvants is not related to site or extent of paediatric practice. Use of drugs can be learned easily from reading and discussion or extrapolated from adult practice and is a skill that is highly transferable between practitioners. Development of manual skills requires practice and a supportive environment and as such is not a highly transferable skill so may be more difficult to develop in a relatively isolated setting.

There is a need for further study on the safety profiles and dose–response characteristics of drugs that are added to local anaesthetic solutions for neural block, especially ketamine, which is commonly used but unlicensed, and diamorphine, which is commonly used but little studied. The use of additives in peripheral block needs much investigation. It would also be interesting to see if skill-based knowledge, such as block technique, is affected by hospital variables such as perioperative facilities and policies or skills of one's colleagues. Insight into this has implications for teaching and learning of skills for anaesthetists at all levels.

Acknowledgements

The author would like to thank Clifford Qualls, Professor of Statistics, Emeritus, University of New Mexico and the Audit Department, Royal Manchester Children's Hospital.

References

1 Gunter J. Caudal anesthesia in children: A survey. *Anesthesiology* 1991; **75**: A936

2 Glaufre E, Dalens B, Gombert A. Epidemiology and morbidity of regional anesthesia in children: a one-year prospective survey of the French-Language Society of Pediatric Anesthesiologists. *Anesth Analg* 1996; **83**: 904–12

3 Veyckemans F, Van Obbergh LJ, Gouverneur JM. Lessons from 1100 pediatric caudal blocks in a teaching hospital. *Reg Anesth* 1992; **17**: 119–25

4 Berde CB Convulsions associated with pediatric regional anesthesia. *Anesth Analg* 1992; **75**: 164–6

5 DaConceicao MJ, Coelho L, Khalil M. Ropivacaine 0 25% compared with bupivacaine 0.25% by the caudal route. *Paediatr Anaesth* 1999; **9**: 229–33

6 Reiz S, Haggmark S, Johansson G, Nath S. Cardiotoxicity of ropivacaine—a new amide local anesthetic agent. *Acta Anaesthesiol Scand* 1989; **33**: 93–8

7 Knudsen K, Beckman-Suurkula M, Blomberg S, Sjovall J, Edvardsson N. Central nervous and cardiovascular effects during i v. infusion of ropivacaine, bupivacaine, and placebo in volunteers. *Br J Anaesth* 1997; **78**: 507–14

8 Krane EJ, Jacobsen LE, Lynn AM, *et al.* Caudal morphine for postoperative analgesia in children: a comparison with caudal bupivacaine and intravenous morphine. *Anesth Analg* 1987; **66**· 647–53

9 Lee JJ, Rubin AP. Comparison of a bupivacaine-clonidine mixture with plain bupivacaine for caudal analgesia in children. *Br J Anaesth* 1994; **72**: 258–62

10 Cook B, Grubb DJ, Aldridge LA, *et al.* Comparison of the effects of adrenaline, clonidine and ketamine on the duration of caudal analgesia produced by bupivacaine in children. *Br J Anaesth* 1995; **75**: 698–701

11 Marhofer P, Krenn CG, Plochl W, *et al.* S(+)-Ketamine for caudal block in paediatric anaesthesia. *Br J Anaesth* 2000; **84**: 341–5

12 Kardash K, Schools A, Conception M. Effects of brachial plexus fentanyl on supraclavicular block. *Reg Anesth* 1995; **20**: 311–15

13 Erlacher W, Schuschnig C, Koinig H, *et al.* Clonidine as adjuvant for mepivacaine, ropivacaine and bupivacaine in axillary, perivascular brachial plexus block. *Can J Anaesth* 2001; **48**: 522–5

14 Likar R, Sittl R, Gragger K, *et al.* Peripheral morphine analgesia in dental surgery. *Pain* 1997; **76**: 145–50

15 Allen GC, St Amand MA, Lui AC, Johnson DH, Lindsay MP. Postarthroscopy analgesia with intraarticular bupivacaine/morphine. *Anesthesiology* 1993; **79**: 475–80

British Journal of Anaesthesia 89 (5): 711–14 (2002)

Efficacy of intravenous magnesium in neuropathic pain

S. Brill[1], P. M. Sedgwick[2], W. Hamann[1 3] and P. P. di Vadi[1]*

[1]*Department of Anaesthetics and Pain Management, University Hospital Lewisham, Lewisham High Street, London SE13 6LH, UK.* [2]*Department of Public Health Sciences, St George's Hospital Medical School, London SW17 0RE, UK.* [3]*GKT School of Medicine, Pain Management Unit, Guy's and St Thomas' Hospital, London SE1 9RT, UK*

**Corresponding author*

Background. Postherpetic neuralgia is a complication of acute herpes zoster characterized by severe pain and paraesthesia in the skin area affected by the initial infection. There is evidence that the *N*-methyl-D-aspartate receptor is involved in the development of hypersensitivity states and it is known that magnesium blocks the *N*-methyl-D-aspartate receptor.

Method. A double-blind, placebo-controlled, cross-over study was conducted in which magnesium sulphate was administered as an i.v. infusion. Spontaneous pain was recorded and qualitative sensory testing with cotton wool was performed in seven patients with postherpetic neuralgia before and after the i.v. administration of either magnesium sulphate 30 mg kg^{-1} or saline.

Results. During the administration, pain scores were significantly lower for magnesium compared with placebo at 20 and 30 min (P=0.016) but not at 10 min. I.V. magnesium sulphate was safe, well-tolerated and effective in patients with postherpetic neuralgia.

Conclusion. The present study supports the concept that the *N*-methyl-D-aspartate receptor is involved in the control of postherpetic neuralgia.

Br J Anaesth 2002; **89**: 711–14

Keywords: pain, neuropathic; pain, postherpetic neuralgia

Accepted for publication: May 24, 2002

Postherpetic neuralgia (PHN) is characterized by pain that persists for more than a month after the healing of acute herpes zoster (HZ) lesions.[1] It represents an increasing clinical problem in the elderly population, with a prevalence reaching 75% in patients over 70 yr who have previously had HZ infection.[2]

The typical features of PHN are burning, aching or itching and continuous pain, with additional sharp and shooting components, often associated with hyperalgesia and allodynia. PHN is the consequence of the extensive peripheral and spinal damage caused by the reactivation of the dormant virus.[3] Continuous activation of C-nociceptor fibres causes the release of glutamate from central terminals acting on the amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and the *N*-methyl-D-aspartate (NMDA) receptor.[4]

The NMDA receptor plays an important role in the mechanisms underlying central sensitization (wind-up) in the spinal cord and is critically important for the establishment of several chronic neuropathic pain states.[5] In its inactive state, it is blocked by the presence of a centrally positioned magnesium ion.[6] Afferent activity in nociceptor fibres dislodges the central magnesium ion from the NMDA receptor, thus allowing calcium influx into the cell.

The NMDA receptor antagonist ketamine reduces neuropathic pain and allodynia in patients with chronic PHN.[7] However, the psychomimetic side-effects limit its use in clinical practice.[8]

Magnesium has been shown to exert a physiological block of the ion channel on the NMDA receptor, preventing extracellular calcium ions from entering the cell and contributing to secondary neuronal changes.[9] This double-blind, placebo-controlled, cross-over study evaluated the analgesic properties of magnesium sulphate in patients with PHN.

Methods

Seven patients with PHN, who had not previously responded to conventional treatment with anticonvulsants

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Table 1 Individual patient characteristics. P=placebo; M=magnesium sulphate

Age (yr)	Gender	Group	Ethnicity	HZ (yr)	PHN	Pain	Dynamic allodynia
76	F	P/M	Caucasian	3	Lumbar	+	–
53	F	P/M	Caucasian	4	Thoracic	+	+
76	M	P/M	Caucasian	1.5	Trigeminal	+	–
69	M	M/P	Black	3	Thoracic	+	+
81	F	P/M	Caucasian	0.9	Thoracic	+	+
76	F	M/P	Caucasian	0.8	Cervical	+	+
61	F	P/M	Caucasian	0.9	Thoracic	+	+

Table 2 Pain scores for the difference between magnesium and placebo within individuals at baseline and 10, 20 and 30 min for the seven patients The 95% confidence interval is that for the median difference between placebo and magnesium within individuals

	Baseline	10 min	20 min	30 min
Mean	0.0	1.9	2.4	3.1
Standard deviation	1.00	1.95	1.81	2.48
Median	0	1	2	2
Minimum	–2	0	1	1
Maximum	1	5	5	7
95% confidence interval		0–5	1–5	1–7
P value		0.063	0.017	0.017

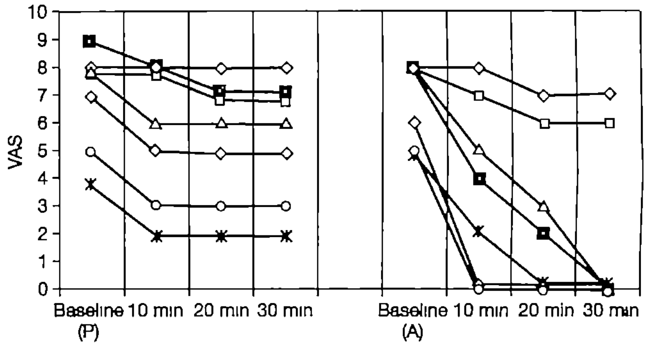


Fig 1 Individual pain scores for the seven patients during the 30 min infusion of placebo (P) and magnesium (A).

and tricyclic antidepressants, were assigned randomly to receive magnesium sulphate first and placebo second or vice versa with a wash-out period of 1 week in between. Randomization was achieved with random number tables. Saline and magnesium solutions were similar in appearance and volume. Both the patient and the assessor were blinded to treatment. The study protocol was approved by the Hospital Ethical Committee and by the Medicines Control Agency of the UK, and informed patient consent was obtained.

Patients with cardiac failure (New York Heart Association grade III or IV), atrioventricular conduction block (grade II or III), serum creatinine in excess of 110 mol litre^{-1} and severe liver disease were excluded from the study. Subjects above 18 yr of age with PHN for more than 3 months after healing of the HZ rash and showing a pain score of ≥4 on a numerical visual analogue scale (VAS) (0=no pain, 10=worst possible pain) were assigned randomly to receive either an i.v. infusion of 0.9% saline 100 ml or magnesium sulphate 30 mg kg^{-1} (magnesium 0.06 mmol kg^{-1}) over 30 min (the required amount was added as a 50% magnesium sulphate solution to 100 ml of saline). One week later, the other solution was infused. The magnesium concentration used in the study was well below what is widely administered in suspected myocardial infarction, for the emergency treatment of serious arrhythmias and to prevent recurrent seizures in eclampsia.

The severity of pain was recorded using a numeric VAS at baseline and at 10, 20 and 30 min during the infusion. The patients were also asked about the degree of pain relief at the time of discharge, 1 h later and the following morning. Mechanical stimulation with cotton wool to test for mechanical dynamic allodynia was performed before and immediately after the infusions. Serum magnesium concentrations were measured before the start of the study and found to be within normal limits in all patients.

The Wilcoxon signed rank test was used to ascertain if pain scores were the same between magnesium and placebo within individuals, sequentially in time, at 10, 20 and 30 min during the infusion. As three sequential statistical tests were performed, Bonferroni's correction factor was applied to adjust for multiple testing. The critical significance level was adjusted from 0.05 to 0.017 accordingly. All reported *P*-values are two-tailed.

Results

Patient characteristics are shown in Table 1. The minimum duration of PHN in our sample was 8 months.

The mean (SD) pain score during the magnesium infusion fell from 6.7 (1.7) at baseline to 1.9 (3.2) at 30 min. The difference in pain score between placebo and magnesium within individuals was not significant at 10 min (P=0.063) but was significant at 20 (P=0.016) and 30 min (P=0.016) (Table 2). Five out of seven patients reported complete pain relief after the magnesium infusion and none after the saline infusion (Fig. 1), which lasted until hospital discharge 1 h later. The patients were contacted by telephone the following day. All of them reported that the pain had come back during the previous evening. The same five patients who achieved pain relief had dynamic allodynia, which was unchanged after either infusion.

No adverse events were reported during the magnesium sulphate infusion, apart from a mild feeling of warmth at the site of the injection. Throughout the magnesium infusion, heart rate and arterial blood pressure did not change by more than 15% of baseline values for all patients. Arterial oxygen saturation was stable and did not fall below 97%.

Discussion

Postherpetic neuralgia is a condition that is not always responsive to established treatments, such as antidepressants, antiepileptics and opioids. Furthermore, fewer than 50% of patients with PHN experience pain relief in the absence of unacceptable adverse effects.[10] The pathophysiology of PHN includes both peripheral and central mechanisms. Three subtypes of PHN have been proposed recently: (i) deafferented allodynic; (ii) deafferented non-allodynic; and (iii) irritable nociceptor.[11] Additionally, patients may also present static (pressure-evoked) and/or dynamic (brush-evoked) allodynia. Our patient population was small and not a representative sample of the three subgroups. Therefore, it was not possible to look for selective effectiveness of magnesium between the above subtypes.

Magnesium could be expected to modulate neuropathic pain by blocking the NMDA receptor calcium ionophore. This mechanism may prevent nociceptive-associated central sensitization[5] and lessen the increased activity of wide-dynamic range neurones in the dorsal horn after prolonged activation. Assuming extracellular distribution of magnesium, plasma concentrations in our patients would have risen by approximately a third during the infusion, causing a block of the NMDA receptor with subsequent pain relief.

Magnesium therapy has been shown to be potentially beneficial in eclampsia[12] and, more recently, in headache[13 14] and acute migraine attacks.[15] The systemic and intrathecal injection of magnesium suppresses neuropathic pain responses in different rat models.[15–21] In man, an i.v. infusion of magnesium sulphate caused a reduction of postoperative analgesic requirement[22–24] and an oral daily dose of magnesium sulphate was shown to be effective in neuropathic pain.[25]

In our study, magnesium clearly reduced PHN pain in comparison with placebo. This effect was initially observed 10 min after the start of the infusion, reaching statistical significance after 20 min. The majority of subjects achieved substantial pain relief during the magnesium infusion, whereas none of them had any relief during the placebo infusion. Although the study had a small sample size, its cross-over design increased its statistical power.

We did not observe an inhibitory effect on allodynia, as would have been predicted from postsynaptic action of magnesium. However, dynamic allodynia does not rely on the wind-up effect, which is mediated through the NMDA receptor. It is therefore not surprising that there was a different response to i.v. magnesium between ongoing pain and pain caused by brief mechanical stimulation.

Our results show that the physiological action of magnesium on NMDA receptors can be translated into a viable concept for pain control in some patients with PHN.

References

1 Rowbotham MC, Petersen KL. Zoster-associated pain and neural dysfunction. *Pain* 2001; **93**: 1–5

2 Kost RG, Strauss SE. Postherpetic neuralgia—pathogenesis, treatment, and prevention. *New Engl J Med* 1996, **335**: 32–42

3 Mahalingam R, Wellish M, Wolf W, *et al.* Latent varicella-zoster viral DNA in human trigeminal and thoracic ganglia *New Engl J Med* 1990; **323**: 627–31

4 Nurmikko T. Pathophysiology of acute herpes zoster and postherpetic neuralgia. *Pain Forum* 1998; **4**: 238–40

5 Woolf CJ, Thompson WN. The induction and maintenance of central sensitisation is dependent on *N*-methyl-D-aspartic acid receptor activation: implications for the treatment of post-injury pain hypersensitivity states. *Pain* 1991; **44**: 298–9

6 Dickenson AH. NMDA receptor antagonists as analgesics. In: Fields HL, Liebeskind JC. *Progress in Pain Research and Management, Volume 1.* Seattle: IASP Press, 1994, 173–87

7 Hoffmann V, Coppejans H, Vercauteren M, Adriaensen H. Successful treatment of postherpetic neuralgia with oral ketamine. *Clin J Pain* 1994; **10**: 240–2

8 Byas-Smith MG, Max MB, Gracely RH, Bennett GJ. Intravenous ketamine and alfentanil in patients with chronic causalgic pain and allodynia [abstract]. *7th World Congress on Pain* 1993; 454–5

9 Fawcet WJ, Haxby EJ, Male DA. Magnesium: physiology and pharmacology. *Br J Anaesth* 1999; **83**: 302–20

10 Kingery WS A critical review of controlled clinical trials for peripheral neuropathic pain and complex regional pain syndromes. *Pain* 1997; **73**: 123–39

11 Rowbotham MC, Petersen KL, Fields HL. Is postherpetic neuralgia more than one disorder? *Pain Forum* 1998, **7**: 231–7

12 Eclampsia Trial Collaborative Group. Which anticonvulsant for women with preeclampsia? Evidence from the Collaborative Eclampsia Trial. *Lancet* 1995; **345**: 1455–63

13 Ginder S, Oatman B, Pollack M. A prospective study of i.v magnesium and i.v. prochlorperazine in the treatment of headaches. *J Emerg Med* 2000; **18**: 311–5

14 Mauskop A, Altura BT, Cracco RQ, Altura BM. Intravenous magnesium sulfate alleviates headaches of various types. *Headache* 1996; **36**: 154–60

15 Demirkaya S, Vural O, Dora B, Topcuoglu MA. Efficacy of intravenous magnesium sulphate in the treatment of acute migraine attacks. *Headache* 2001; **41**: 171–7

16 Begon S, Pickering G, Eschalier A, Dubray C Magnesium and MK-801 have a similar effect in two experimental models of neuropathic pain. *Brain Res* 2000; **887**: 436–9

17 Feria M, Abad F, Sanchez A, Abreu P. Magnesium sulphate injected subcutaneously suppresses autonomy in peripherally deafferented rats. *Pain* 1993; **53**: 287–93

18 Karesawa S, Ishizaki K, Goto F. The effect of intrathecal administration of magnesium sulphate in rats. *Anaesthesia* 1998; **53**: 879–86

19 Takano Y, Sato E, Kaneko T, Sato I. Antihyperalgesic effects of intrathecally administered magnesium sulfate in rats. *Pain* 2000; **84**: 175–9

20 Tsai P, Cheng J, Marsala M, Lin C, Wen G, Yang LC. Intrathecal magnesium sulphate attenuates algogenic behavior and spinal amino acids release after kainic acid receptor activation in rats. *Neuroscience Lett* 2001; **301**: 115–8

21 Xiao WH, Bennett GJ. Magnesium suppresses neuropathic pain responses in rats via a spinal site of action. *Brain Res* 1994; **666**: 168–172

22 Koinig H, Wallner T, Marhofer P, Andel H, Horauf K, Mayer N. Magnesium sulphate reduces intra-and postoperative analgesic requirements. *Anesth Analg* 1998; **87**: 206–10

23 Schultz-Stubner S, Wettmann G, Reyle-Hahn SM, Rossaint R. Magnesium as part of balanced general anaesthesia with propofol, remifentanil and mivacurium: a double-blind, randomised prospective study in 50 patients. *Eur J Anaesthesiol* 1991; **18**: 723–9

24 Tramer MR, Schneider J, Marti RA, Rifat K. Role of magnesium sulfate in postoperative analgesia. *Anesthesiology* 1996; **84**: 340–7

25 Crosby V, Wilcock A, Corcoran R. The safety and efficacy of a single dose (500 mg or 1 g) of intravenous magnesium sulfate in neuropathic pain poorly responsive to strong opioid analgesics in patients with cancer. *J Pain Symptom Manage* 2000; **19**: 35–9

British Journal of Anaesthesia 89 (5): 715–21 (2002)

Platelet function point-of-care tests in post-bypass cardiac surgery: are they relevant?

F. Forestier[1]*, A. Coiffic[1]*, C. Mouton[2], D. Ekouevi[3], G. Chêne[3] and G. Janvier[1]

[1]Department of Anaesthesia II and [2]Haemobiology Laboratory, Hôpital cardiologique, CHU de Bordeaux, Avenue de Magellan, F-33604 Pessac cedex, France. [3]INSERM Unit 330, Victor Segalen Bordeaux 2 University, Bordeaux, France

**Corresponding author*

Background. Platelet dysfunction is an important cause of excessive bleeding after cardiac surgery. We assessed two platelet function point-of-care tests: the platelet function analyser (PFA-100) and the Hemostatus™ in patients with and without excessive bleeding after cardiac surgery with cardiopulmonary bypass.

Methods. Mediastinal chest tube drainage (MCTD) was measured for the first 6 h in the intensive care unit (ICU). Haematology and coagulation tests were done on arrival in the ICU, and when excessive bleeding occurred (MCTD >1 ml kg^{-1} h^{-1}) or after 3 h.

Results. Eighteen patients bled excessively and 27 had normal MCTD. Hemostatus measurements were prolonged in those with excessive bleeding compared with the normal group. The times for PFA-100 adenosine diphosphate (ADP) and epinephrine were 91 *vs* 71 s (*P*=0.004) and 155 *vs* 114 s (*P*=0.02) in the bleeding and normal group s, respectively. None of the Hemostatus or PFA-100 values correlated with total MCTD. Depending on the agonist used, maximum aggregation was 33–81% and 52–86% in bleeding and normal groups, respectively. Only poor correlations were found between PFA-100 epinephrine and maximum aggregation in response to ADP (*r*=–0.52, *P*=0.03) or to collagen (*r*=–0.48, *P*=0.04).

Conclusion. Patients bleeding excessively in the ICU had abnormal measurements in point-of-care tests without a dramatic decrease in aggregation. Except for patients with increased risk of postbypass bleeding, point-of-care tests are not useful for routine use after cardiac surgery.

Br J Anaesth 2002; **89**: 715–21

Keywords: blood, loss; blood, platelets; monitoring, point-of-care test; surgery, cardiovascular

Accepted for publication: September 12, 2001

Bleeding is a common complication of cardiac surgery with cardiopulmonary bypass (CPB), which can require transfusion of blood products and, in 3–6% of cases, mediastinal re-exploration.[1] Of the causes of excessive bleeding, platelet dysfunction is considered to be the most important in the early postoperative period.

Two *in vitro* coagulation tests, the Hemostatus test and the platelet function analyser (PFA-100) are designed to provide simple and rapid assessment of platelet function, but their ability to predict excessive blood loss associated with CPB remains uncertain.[2–6] However, the relevance of these tests when bleeding occurs in the intensive care unit (ICU) has been investigated less.[7 8] We hypothesize that these point-of-care tests could help to detect poor platelet function and, with the help of guidelines,[9 10] reduce the considerable variation in transfusion practice between institutions.[11] We compared the PFA-100 and Hemostatus after cardiac surgery with CPB, in patients with and without excessive bleeding, in comparison with platelet aggregometry results.

Methods

The study was approved by our Institutional Ethics Committee. After obtaining informed consent, we recruited adult patients undergoing first-time cardiac surgery with CPB. We excluded patients who had taken antiplatelet drugs within 7 days of the operation, those on heparin or

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

anticoagulant therapy, or with bleeding diathesis or conditions that could affect platelet function. Because fibrinolytic activity can develop quickly, with maximal plasma levels of fibrin degradation products 30 min after infusion of protamine,[12] patients who had diffuse bleeding from the surgical site without any identified source, after neutralization of heparin, were also excluded.

Study groups

Patients were recruited consecutively. We defined patients with excessive bleeding if they had mediastinal chest tube drainage (MCTD) >1 ml kg^{-1} h^{-1} for at least 1 h during the first 6 h after surgery. Patients were studied as those with and without excessive bleeding.

Operative details

Anaesthesia was induced and maintained with i.v. propofol (target controlled infusion), sufentanil citrate and atracurium. An ultra-low prophylactic dose of aprotinin (5×10^5 KIU) was administered before skin incision, and again during initiation of CPB. Patients were given heparin 300 UI kg^{-1} before CPB, and the activated clotting time (ACT), using kaolin as the activating agent (Medtronic, ACT II HemoTec, Rueil Malmaison, France) was maintained during CPB at a value greater than 450 s with additional doses of heparin as required. The extracorporeal circuit was primed with 1000–1200 ml lactated Ringer's solution (Bioluz, St Jean de Luz, France) containing 4000 units of heparin. A membrane oxygenator was used and flows of 1.8–2.2 litre min^{-1} m^{-2} were obtained with a roller pump (Stöckert Instrumente, Munich, Germany) under mild hypothermic or normothermic conditions. After discontinuation of CPB, anticoagulation was reversed with protamine sulphate. Blood remaining in the CPB circuit was collected and infused into the patient before transfer to the ICU. Our practice was to maintain the haematocrit above 25% after CPB as long as haemodynamic stability was maintained. Mediastinal blood loss was measured by the nurses every hour after arrival in the ICU. If bleeding was excessive, coagulopathy was treated as follows: (i) with additional protamine if the thrombin time was longer than 30 s, (ii) with 2–4 units of virally inactivated fresh frozen plasma if the activated partial thromboplastin time (aPTT) was greater than 50 s (1.5 times the normal value of our laboratory), (iii) with 8 units of platelet concentrate if the platelet count was less than $50\,000 \times 10^9$ litre^{-1}.

Haematologic assays

Native whole-blood samples were taken from a radial arterial catheter on arrival in the ICU for all patients (T_1), and when excessive bleeding was diagnosed or after 3 h in the ICU (T_2). Haemoglobin concentration, haematocrit and platelet count (Coulter Diagnostics, Villepinte, France) were measured in the two groups at T_1 and T_2. Anti-Xa activity was measured at T_1 in all patients. A routine coagulation profile including prothrombin time, aPTT and fibrinogen concentration was done in all patients at T_1 and T_2.

The Hemostatus test was performed at T_2 using the Hepcon/Hemostatus™ apparatus (Medtronic, Rueil-Malmaison, France). Six channels with cartridges containing 0.05 M calcium chloride, kaolin 4% (w/v), and heparin 3 IU ml^{-1} were used. A syringe containing 3 ml native whole blood was mounted on the machine, and 0.35 ml automatically dispensed into each of six channels of the cartridge to measure the platelet-activated clotting time (PACT) in the presence and absence of platelet activating factor (PAF). Channels 1 and 2 did not contain PAF (control ACT) whereas channels 3–6 contained increasing concentrations of PAF (1.25, 6.25, 12.5 and 150 nM). Heparin was used to increase the sensitivity of the method by prolonging the Hemostatus values. Mechanical shear stress activation was obtained by a plunger mechanism contained in each channel. Hemostatus values were expressed directly as the clotting time (s).

The closure time was measured at T_2 with the PFA-100 (Dade-Behring Inc., Miami, FL, USA). This device comprises a microprocessor-controlled instrument and disposable test cartridges with a bioactive membrane coated with type-I equine collagen and, depending on the cartridge, epinephrine or adenosine diphosphate (ADP). The instrument uses a constant vacuum to aspirate a citrated whole-blood sample introduced into the cartridge, through a capillary and a microscopic aperture cut into the membrane. The time from the start of the test until the occlusion of the aperture by a platelet plug was reported as the PFA-100 closure time (s).

Part of the citrated whole-blood samples (4.5 ml) taken from each patient at T_2 was used for platelet aggregometry. Samples were centrifuged at 180 *g* for 10 min at room temperature to separate platelet-rich plasma. Platelet aggregation of platelet-rich plasma was assessed using the PAP-4 aggregometer (PAP-4 model; BIO/DATA Corporation, Paris, France), in the presence of different commonly used chemical activators: ADP (5 μm litre^{-1}, Sygma A88-5.3), arachidonic acid (500 μm ml^{-1}, Tauzart et Matignon, France), collagen (16 μg ml^{-1}, Sygma A88.6), epinephrine (8 μm litre^{-1}, Sygma A88.5-5), and ristocetin (1.5 mg ml^{-1}, Stago501). Maximum aggregation (MA) was registered for each agonist after 5 min.

Physicians were unaware of the results of Hemostatus, PFA-100 and aggregometry when treating the excessive MCTD.

Data collection

Patient characteristics and perioperative data were collected on a standardized questionnaire, and included age, sex, height, weight, duration of CPB, haematology and haemostasis results, doses of heparin and protamine, core body temperature during the stay in the ICU, hourly MCTD for the 6 h after surgery, intravascular volume replacement with colloids (medium-molecular weight hydroxyethyl starch solution, 200 000 Da, degree of substitution 0.6), blood products given, and treatment with aprotinin (10^6 KIU) as part of our treatment plan to control postbypass bleeding.

Statistical analysis

Qualitative variables were compared between bleeding and non-bleeding groups using Fisher's exact test, and continuous variables using the student's *t* test or the Wilcoxon rank-sum test. Comparisons of Hemostatus and PFA-100 values between bleeding and non-bleeding groups were adjusted for haemoglobin concentration and platelet count by logistic regression. Spearman's rank correlation test was used to assess the relationship between Hemostatus and PFA-100 measurements and either platelet aggregation results or total MCTD. $P<0.05$ was considered statistically significant. The statistical analysis was done using STATA® software.

Results

Excessive bleeding occurred in 18 patients and 27 patients did not have excessive bleeding. Age, sex and weight did not differ between groups (Table 1). Surgical procedures did not differ between the groups. Mean duration of CPB was not significantly different: 77 min in the bleeding group *vs* 83 min in the normal group. Mean heparin and protamine doses did not differ between the two groups.

Figure 1 shows the changes of MCTD and core body temperature over time in the ICU. In bleeding patients, MCTD reached the maximal value (204 ml) 2 h after surgery, then sharply decreased during the third hour and, according to our criterion, returned to normal bleeding rate (60 ml) after 4 h. Nine patients started to bleed excessively during the first hour, and nine others during the second hour in the ICU. The median duration of bleeding was 3 h in this group. Median blood loss in the first 6 h was 580 ml in the bleeding group and 125 ml in the non-bleeding group ($P<0.001$). The mean time of T_2 was 156 (SD 55) min in the bleeding group and 192 (33) min in the normal group. Core body temperature of patients with bleeding was lower than in those without bleeding, especially during the third hour after surgery, but no statistically significant difference was shown during the stay in the ICU. All patients reached a core body temperature of 37°C by 4 h.

Treatment of excessive bleeding is shown in Table 2. Median volumes of red blood cells and virally inactivated fresh frozen plasma given were 460 and 200 ml, respectively. No patients required surgical re-exploration.

Table 1 Characteristics of bleeding and normal patients CPB, cardiopulmonary bypass

Characteristic	**Bleeding patients (n=18)**	**Normal patients (n=27)**
Mean age (range) (years)	67 (50–82)	67 (46–77)
Male (%)	83	74
Mean (SD) weight (kg)	73 (3)	72 (2)
Type of surgery (%)		
Coronary artery bypass grafting	44	48
Valve	33	44
Combined procedure	22	7
Mean (SD) duration of CPB (min)	77 (6)	84 (5)
Median heparin dose (×10^3 IU) (25th–75th percentile)	25 (21–30)	24 (22–27)
Mean (SD) protamine dose (mg)	27 (16)	23 (11)

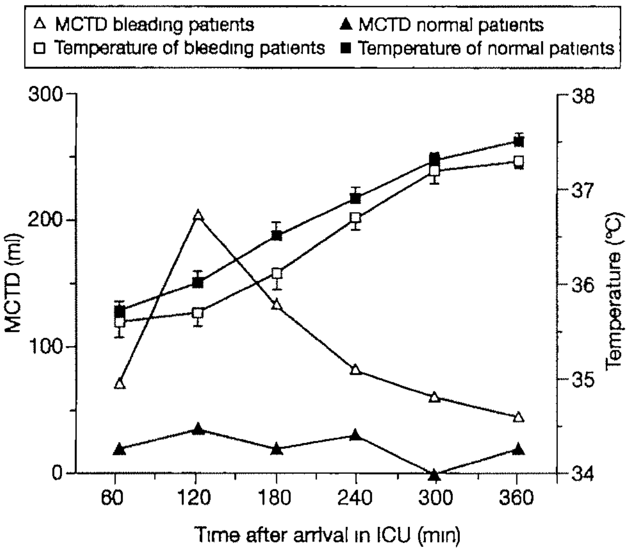


Fig 1 Median mediastinal chest tube drainage (MCTD) and mean (SD) core body temperature over time in the intensive care unit in bleeding and normal patients.

Table 3 summarizes haemoglobin concentration, platelet count and routine coagulation values at T_1 and T_2. At T_1, differences were found between bleeding and normal groups in haemoglobin concentration (10.7 *vs* 11.1 g litre^{-1}, $P<0.05$), and mean fibrinogen concentration (2.5 *vs* 3.3 g litre^{-1}, $P<0.01$). Mean platelet count did not differ between the two groups on arrival in the ICU (127 *vs* 154×10^9 litre^{-1}, respectively). At T_2, all haematology values reported in Table 3 were significantly less in bleeding patients than in normal patients, except for aPTT, which did not differ between the two groups (46.7 *vs* 43.4 s, respectively).

The results of Hemostatus and PFA-100 at T_2 are shown in Table 4. In bleeding patients, PACT values were significantly prolonged in all channels compared with normal patients, and PFA-100 ADP and epinephrine closure time values reached 91 *vs* 71 s ($P<0.01$) and 155 *vs* 114 s, respectively ($P<0.05$). However, after adjusting PACT and PFA-100 closure time values at T_2 for haemoglobin concentration and platelet count by logistic regression, there was no difference between groups. The Hemostatus or PFA-100 values did not correlate with total MCTD.

Table 5 shows the results of platelet aggregometry performed at T_2 with collagen, ristocetin and arachidonic acid as chemical activators in bleeding and normal patients. Platelet MA was significantly lower in bleeding patients compared with normal patients, in the presence of ADP (50.1 *vs* 61.2%, $P<0.05$) and epinephrine (32.9 *vs* 51.9%, $P<0.05$).

Table 6 shows the relationship between Hemostatus, PFA-100 closure time results and MA in bleeding patients. None of the Hemostatus values correlated with MA. No correlation was found between PFA-100 closure time and MA results except for PFA-100 epinephrine which correlated with MA in the presence of ADP ($r=-0.52$, $P<0.05$) and collagen ($r=-0.48$, $P=0.05$).

Table 2 Treatment of excessive bleeding in 18 patients. No treatment was given to patients without excessive bleeding. Values in parentheses are 25th–75th percentiles. *The colloid used was 6% medium-molecular-weight hydroxyethyl starch solution (200 000 Da, degree of substitution 0.6)

Treatment	**Bleeding patients** (*n*=18)
Blood products	
Median red blood cells (ml)	460 (0–600)
Median platelets (units)	0 (0–0)
Median virally inactivated fresh frozen plasma (ml)	200 (0–600)
Median aprotinin dose (10^6 KIU)	1 (1–1)
Median colloids (ml)*	500 (0–500)

Discussion

We found that point-of-care tests of platelet function are significantly prolonged when excessive bleeding occurs. These tests did not correlate with total MCTD, and only a weak correlation was found between PFA-100 epinephrine and laboratory-based platelet aggregation. Depending on the agonist used, MA was 33–81% in the bleeding group and 52–86% in the non-bleeding group. No significant difference existed between the groups, except for ADP and epinephrine tests.

Preliminary studies reported a great sensitivity of Hemostatus and PFA-100 tests to major platelet adherence or aggregation abnormalities. With the Hemostatus test, Coiffic and colleagues[13] found impairment of GPIIb–IIIa receptors by c7E3 (chimeric Fab fragments of a murine monoclonal antibody), lengthening the PACT by up to 1500 s, when mean PACT values of the 18 controls ranged from 517 (SD 121) s to 350 (124) s (channels 1 and 2, and 3–6, respectively). Others reported lengthening of PFA-100

Table 3 Haematology measurements in bleeding and normal patients. Data are mean (SD). n.s., not significant

Variable	**Normal range**	**Bleeding patients** (*n*=18)	**Normal patients** (*n*=27)	***P* value**
T1 arrival in ICU				
Haemoglobin concentration (g litre^{-1})	11.5–17.7	10.7 (2.2)	11.1 (1)	<0.05
Haematocrit (%)	37–54	30.4 (0.9)	32.3 (0.7)	n.s.
Platelet count (10^9 litre^{-1})	150–500	127.4 (13)	154.8 (8)	0.07
Prothrombin time (%)	80–100	58.2 (1.9)	63.1 (1.7)	0.07
Activated partial thomboplastin time (s)	26–42	43.4 (6.6)	43.4 (5.9)	n.s.
Fibrinogen concentration (g litre^{-1})	>2	2.5 (0.5)	3.3 (1)	<0.01
Anti-Xa activity (IU ml^{-1})		0.03 (0.04)	0.07 (0.06)	<0.05
T2: when bleeding occurred (bleeding patients) or 3 h after surgery (normal patients)				
Haemoglobin concentration (g litre^{-1})	11.5–17.7	10.2 (0.27)	12.2 (0.28)	<0.001
Haematocrit (%)	37–54	29.9 (0.72)	35.6 (0.8)	<0.001
Platelet count (10^9 litre^{-1})	150–500	145.7 (11)	186.1 (10)	0.01
Prothrombin time (%)	80–100	61.6 (2)	69.5 (2)	0.01
Activated partial thomboplastin time (s)	26–42	46.7 (2.4)	43.4 (1.4)	n.s.
Fibrinogen concentration (g litre^{-1})	>2	2.6 (0.14)	3.7 (0.2)	<0.001

Table 4 Laboratory results for the Hemostatus and PFA-100 at T2. Results obtained in Channel 1–2 were obtained from the first two channels without platelet activating factor. *Adjusted for haemoglobin concentration and platelet count. Values in parentheses are 25th–75th percentiles

Variable	**Bleeding patients** (*n*=18)	**Normal patients** (*n*=27)	**Unadjusted *P* value**	**Adjusted *P* value***
Hemostatus median platelet-activated clotting time (s)				
Channel 1–2	620 (461–860)	410 (327–510)	<0.001	0.08
Channel 3	517 (451–693)	424 (362–499)	0.005	0.16
Channel 4	389.5 (336–459)	322 (276–369)	0.001	0.17
Channel 5	353 (299–389)	301 (250–334)	0.009	0.35
Channel 6	284 (266–352)	252 (226–287)	0.014	0.07
PFA-100. median closure time (s)				
PFA-100 ADP	91 (76–108)	71 (60–80)	0.004	0.47
PFA-100 epinephrine	155 (114–227)	114 (94–130)	0.02	0.18

closure time, by impairment of von Willebrand factor or inhibition of GPIb and GPIIb–IIIa receptors.[14 15] In the present study, in spite of a significant difference between the groups, Hemostatus and PFA-100 values lay in ranges described for healthy volunteers.[16-17] These data should be compared with laboratory-based platelet aggregation tests that are very sensitive to the impairment of platelet function after CPB.[18] Although these tests are highly dependent on sample preparation and operator,[19] they do not show a severe impairment of GPIb and IIb–IIIa receptors of patients bleeding excessively in this study. MA in response to ADP and epinephrine differed at T_2 but this is probably not clinically significant. This result may be explained by the average time of T_2 in this study since platelet aggregation is known to recover from the second hour after surgery, and to return to baseline levels 4 h after CPB.[20] MA in response to collagen and arachidonic acid did not differ between groups, and the response to ristocetin fits well with normal functional responses of GPIb and GPIIb–IIIa. For these reasons, major abnormalities of platelet membrane receptors are unlikely to be responsible for the slight increase of Hemostatus and PFA-100 measurements observed in patients with bleeding in the present study. On the whole, our results failed to show a correlation between point-of-care tests and aggregometry in patients with bleeding, especially between PFA-100 epinephrine and platelet aggregometry induced by epinephrine. This may be explained by the fact that aggregometry is performed on platelet-rich plasma, while the PFA-100 closure time is done on native whole-blood samples and under high shear conditions very different from those of platelet aggregometry.

Table 5 Laboratory results for platelet aggregometry at T_2 – maximum aggregation (%). Data are mean (SD) n.s.=not significant

	Bleeding patients (*n*=18)	Normal patients (*n*=27)	*P* value
ADP	50 (15)	61 (18)	<0.05
Collagen	42 (24)	43 (29)	n.s.
Arachidonic acid	47 (24)	57 (30)	n.s.
Epinephrine	33 (23)	52 (26)	<0.05
Ristocetin	82 (11)	86 (14)	n.s.

Other factors, apart from platelet defects, can affect these point-of-care tests on whole blood, such as altered haematocrit and platelet count.[13 21 22] Red blood cells can also affect platelet function, related to stimulation of platelet production of thromboxane A_2,[23] or to shear-induced release of ADP when haematocrit is 25–35%.[24] Hemostatus should reliably detect platelet dysfunction only if the platelet count is greater than $50–70\times10^9$ litre^{-1},[13 17] and PFA-100 if the platelet count exceeds 100×10^9 litre^{-1} and the haematocrit exceeds 30%.[21] To our knowledge, neither the manufacturers nor the literature provide information about correction of Hemostatus results for altered haematocrit. In our study, platelet count and haematocrit were significantly lower in bleeding patients, without exceeding the limits of interpretation of the point-of-care tests. However, because haemodilution is common after cardiac surgery, we investigated the possibility that differences between groups could be reduced by adjusting Hemostatus and PFA-100 values for haemoglobin concentration and platelet count by logistic regression. Our results suggest these two variables are an important source of variation in the results of Hemostatus and PFA-100, and could explain the differences between bleeding and normal patients.

The use of aprotinin in the present study may be questioned too, since the protective mechanism of aprotinin on platelet function is controversial.[25 26] However, the initial elimination half-life of aprotinin is about 1 h, so platelet function is unlikely to be affected by the ultra-low prophylactic dose administered before skin incision and during initiation of CPB. Furthermore, blood samples for aggregometry and point-of-care tests were collected before any possible therapeutic use of aprotinin, as part of our treatment plan to control postbypass bleeding in the ICU.

Preliminary reports on the ability of Hemostatus and PFA-100 tests to predict excessive blood loss associated with CPB gave mixed results.[2–5] Our primary hypothesis

Table 6 Relationship between Hemostatus (platelet-activated clotting time [PACT]), PFA-100 (closure time) and platelet aggregometry in bleeding patients (*n*=18)

	Maximum aggregation									
	ADP		Collagen		Arachidonic acid		Epinephrine		Ristocetin	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
PFA-100										
ADP	–0.057	0.82	0.084	0.74	–0.188	0.46	0.110	0.67	0.079	0.76
Epinephrine	–0.502	0.04	–0.481	0.05	–0.420	0.08	–0.399	0.10	0.104	0.69
Hemostatus										
Channel 1–2	–0.371	0.13	–0.204	0.42	–0.315	0.21	–0.246	0.33	–0.204	0.43
Channel 3	–0.305	0.22	–0.200	0.43	–0.395	0.11	–0.076	0.77	–0.069	0.80
Channel 4	–0.086	0.74	0.006	0.98	–0.147	0.56	–0.009	0.97	–0.148	0.57
Channel 5	–0.054	0.83	0.071	0.78	–0.147	0.56	0.067	0.79	–0.24	0.36
Channel 6	–0.133	0.6	0.008	0.98	–0.275	0.27	–0.029	0.91	–0.293	0.26

was that these tests could detect a platelet function defect, and be used to rationalize transfusion practices. The fact that no relationship exists between Hemostatus and PFA-100 results and total MCTD does not necessarily mean that these tests are not specific and reliable, because defects after bypass are generally thought to be secondary to the activation, consumption or dilution of several constituents of haemostasis. We found discrepancies in the results of point-of-care tests of bleeding and normal groups, and an overall lack of correlation with MCTD. In patients with a low risk for postoperative bleeding, who account for about 60% of patients, the routine use of Hemostatus and PFA-100 is unlikely to improve transfusion practice. However, these tests would be more efficient when patients are at high risk of perioperative bleeding, for example patients with von Willebrand disease.[27 28]

In our study, which excluded patients receiving antiplatelet drugs, anticoagulant therapy or a preoperative bleeding diathesis, we conclude that these point-of-care tests should not be used for routine evaluation when excessive bleeding occurs after cardiac surgery. Clinical assessment and transfusion algorithms, with continuous assessment of mediastinal drainage, are essential in modern management. However, because they can detect severe platelet dysfunction, further studies are necessary to assess these tests for the management of patients with von Willebrand disease or receiving anti-GPIIb–IIIa drugs.

Acknowledgements

The authors thank Dr P Nurden and A. Feyler for assistance.

References

1 Spiess BD, Gillies BS, Chandler W, Verrier E. Changes in transfusion therapy and reexploration rate after institution of a blood management program in cardiac surgical patients. *J Cardiothorac Vasc Anesth* 1995; **9**: 168–73

2 Despotis GJ, Levine V, Filos KS, *et al.* Evaluation of a new point-of-care test that measures PAF-mediated acceleration of coagulation in cardiac surgical patients. *Anesthesiology* 1996; **85**: 1311–23

3 Wahba A, Sander S, Birnbaum DE. Are in-vitro platelet function tests useful in predicting blood loss following open heart surgery? *Thorac Cardiovasc Surg* 1998; **46**: 228–31

4 Ereth MH, Nuttall GA, Klindworth JT, *et al.* Does the platelet-activated clotting test (HemoSTATUS) predict blood loss and platelet dysfunction associated with cardiopulmonary bypass? *Anesth Analg* 1997; **85**: 259–64

5 Ereth MH, Nuttall GA, Santrach PJ, *et al.* The relation between the platelet-activated clotting test (HemoSTATUS) and blood loss after cardiopulmonary bypass. *Anesthesiology* 1998; **88**: 962–9

6 Shore-Lesserson L, Ammar T, DePerio M, *et al.* Platelet-activated clotting time does not measure platelet reactivity during cardiac surgery. *Anesthesiology* 1999; **91**: 362–8

7 Nuttall GA, Oliver WC, Ereth MH, Santrach PJ. Coagulation tests predict bleeding after cardiopulmonary bypass [see comments]. *J Cardiothorac Vasc Anesth* 1997; **11**: 815–23

8 Dietrich GV, Schueck R, Menges T, *et al.* Comparison of four methods for the determination of platelet function in whole blood in cardiac surgery. *Thromb Res* 1998; **89**: 295–301

9 Consensus conference. Platelet transfusion therapy. *JAMA* 1987; **257**: 1777–80

10 Goodnough LT, Johnston MF, Ramsey G, *et al.* Guidelines for transfusion support in patients undergoing coronary artery bypass grafting. Transfusion Practices Committee of the American Association of Blood Banks. *Ann Thorac Surg* 1990; **50**: 675–83

11 Stover EP, Siegel LC, Parks R, *et al.* Variability in transfusion practice for coronary artery bypass surgery persists despite national consensus guidelines: a 24-institution study. Institutions of the Multicenter Study of Perioperative Ischemia Research Group. *Anesthesiology* 1998; **88**: 327–33

12 Lu H, Du Buit C, Soria J, *et al.* Postoperative hemostasis and fibrinolysis in patients undergoing cardiopulmonary bypass with or without aprotinin therapy. *Thromb Haemost* 1994; **72**: 438–43

13 Coiffic A, Cazes E, Janvier G, *et al.* Inhibition of platelet aggregation by abciximab but not by aspirin can be detected by a new point-of-care test, the hemostatus. *Thromb Res* 1999; **95**: 83–91

14 Kundu SK, Heilmann EJ, Sio R, *et al.* Description of an *in vitro* platelet function analyzer–PFA-100. *Semin Thromb Hemost* 1995; **21**: 106–12

15 Harrison P, Robinson MS, Mackie IJ, *et al.* Performance of the platelet function analyser PFA-100 in testing abnormalities of primary haemostasis. *Blood Coagul Fibrinolysis* 1999; **10**: 25–31

16 Mammen EF, Alshameeri RS, Comp PC. Preliminary data from a field trial of the PFA-100 system. *Semin Thromb Hemost* 1995; **21**: 113–21

17 Despotis GJ, Ikonomakou S, Levine V, *et al.* Effects of platelets and white blood cells and antiplatelet agent C7E3 (Reopro) on a new test of PAF procoagulant activity of whole blood. *Thromb Res* 1997; **86**: 205–19

18 Menys VC, Belcher PR, Noble MI, *et al.* Macroaggregation of platelets in plasma, as distinct from microaggregation in whole blood (and plasma), as determined using optical aggregometry and platelet counting respectively, is specifically impaired following cardiopulmonary bypass in man. *Thromb Haemost* 1994; **72**: 511–8

19 Nicholson NS, Panzer-Knodle SG, Haas NF, *et al.* Assessment of platelet function assays. *Am Heart J* 1998; **135**: S170–8

20 Basora M, Gomar C, Escolar G, *et al.* Platelet function during cardiac surgery and cardiopulmonary bypass with low-dose aprotinin. *J Cardiothorac Vasc Anesth* 1999; **13**: 382–7

21 Lasne D, Fiemeyer A, Chatellier G, *et al.* A study of platelet functions with a new analyzer using high shear stress (PFA 100) in patients undergoing coronary artery bypass graft. *Thromb Haemost* 2000; **84**: 794–9

22 Knofler R, Weissbach G, Kuhlisch E. Platelet function tests in childhood. Measuring aggregation and release reaction in whole blood. *Semin Thromb Hemost* 1998; **24**: 513–21

23 Valeri CR, MacGregor H, Cassidy G, *et al.* Effects of temperature on bleeding time and clotting time in normal male and female volunteers. *Crit Care Med* 1995; **23**: 698–704

24 Alkhamis TM, Beissinger RL, Chediak JR. Artificial surface effect on red blood cells and platelets in laminar shear flow. *Blood* 1990; **75**: 1568–75

25 Huang H, Ding W, Su Z, Zhang W. Mechanism of the preserving effect of aprotinin on platelet function and its use in cardiac surgery. *J Thorac Cardiovasc Surg* 1993; **106**: 11–8

26 Santamaria A, Mateo J, Muniz-Diaz E, *et al.* Platelet function during cardiopulmonary bypass not changed by two different doses of aprotinin. *Haematologica* 2000; **85**: 381–5

27 Favaloro EJ, Facey D, Henniker A. Use of a novel platelet function analyzer (PFA-100) with high sensitivity to disturbances in von Willebrand factor to screen for von Willebrand's disease and other disorders. *Am J Hematol* 1999; **62**: 165–74

28 Cattaneo M, Federici AB, Lecchi A, *et al* Evaluation of the PFA-100 system in the diagnosis and therapeutic monitoring of patients with von Willebrand disease. *Thromb Haemost* 1999; **82**: 35–9

British Journal of Anaesthesia 89 (5)· 722–8 (2002)

Effects of a new modified, balanced hydroxyethyl starch preparation (Hextend®) on measures of coagulation

J. Boldt*, G. Haisch, S. Suttner, B. Kumle and A. Schellhaass

Department of Anesthesiology and Intensive Care Medicine, Klinikum der Stadt Ludwigshafen,
Bremserstrasse 79, D-67063 Ludwigshafen, Germany
**Corresponding author*

Background. Hydroxyethyl starch (HES) may affect blood coagulation. We studied the effects of a modified, balanced, high-molecular weight [mean molecular weight (MW) 550 kDa], high-substituted [degree of substitution (DS) 0.7] HES preparation (Hextend®) on coagulation in patients undergoing major abdominal surgery.

Methods. Patients were allocated randomly to receive Hextend® (n=21), lactated Ringer's solution (RL, n=21) or 6% HES with a low MW (130 kDa) and a low DS (0.4) (n=21). The infusion was started after induction of anaesthesia and continued until the second postoperative day to maintain central venous pressure between 8 and 12 mm Hg. Activated thrombelastography (TEG) was used to assess coagulation. Different activators were used (extrinsic and intrinsic activation of TEG) and aprotinin was added to assess hyperfibrinolytic activity (ApTEG). We measured onset of coagulation [coagulation time (CT=reaction time, r)], the kinetics of clot formation [clot formation time (CFT=coagulation time, k)] and maximum clot firmness (MCF=maximal amplitude, MA). Measurements were performed after induction of anaesthesia, at the end of surgery, 5 h after surgery and on the mornings of the first and second days after surgery.

Results. Significantly more HES 130/0.4 [2590 (SD 260) ml] than Hextend® [1970 (310) ml] was given. Blood loss was greatest in the Hextend® group and did not differ between RL- and HES 130/0.4-treated patients. Baseline TEG data were similar and within the normal range. CT and CFT were greater in the Hextend® group immediately after surgery, 5 h after surgery and on the first day than in the two other groups. ApTEG MCF also changed significantly in the Hextend® patients, indicating more pronounced fibrinolysis. Volume replacement using RL caused moderate hypercoagulability, shown by a decrease in CT.

Conclusion. A modified, balanced high-molecular weight HES with a high degree of substitution (Hextend®) adversely affected measures of coagulation in patients undergoing major abdominal surgery, whereas a preparation with a low MW and low DS affected these measures of haemostasis less. Large amounts of RL decreased the coagulation time.

Br J Anaesth 2002; **89**: 722–8

Keywords: blood, coagulation; blood, volume replacement; surgery, abdominal

Accepted for publication: May 3, 2002

Volume loss from the circulation may be caused by changes in the endothelial barrier and diffuse capillary leakage, in addition to blood loss. Adequate volume replacement appears to be a cornerstone for managing patients undergoing major surgery. Hypovolaemia is an important avoidable cause of organ dysfunction and death.[1] In addition to crystalloids [e.g. saline solution, Ringer lactate (RL)] and the natural colloid human albumin, synthetic colloids such as dextrans, gelatins and hydroxyethyl starch (HES) can be used to treat volume deficit.

Coagulation is often impaired when blood loss occurs during surgery. Haemodilution caused by fluid replacement impairs coagulation by reducing the concentration of clotting factors. The type of fluid used may also affect coagulation. Coagulation changes occur after the use of HES,[2–4] but different HES preparations can have different

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

effects on haemostasis.[5] HES with a high molecular weight (MW) and a high degree of substitution (DS) (hetastarch; MW 450 kDa, DS 0.7) reduced concentrations of VIIIR:Ag and VIIIR:RCo more than HES with lower MW and a lower DS [low-molecular weight (LMW) HES; MW 200–260 kDa, DS 0.5].[6] Abnormal platelet function occurs more often after high-molecular weight (HMW) HES.[7] Reports of HES reducing blood coagulation and increasing bleeding generally relate to giving HMW HES and HES with a high degree of substitution (DS 0.7).[8] Consequently, an HES preparation with a lower MW (130 kDa) and a lower DS (0.4) has been developed to reduce the impairment of coagulation.[9] [10] Another way to reduce this effect is by modifying the HMW HES preparation. Hextend® is a modified, physiologically balanced 6% hetastarch solution (molar substitution 0.7; average MW approximately 670 kDa, mean MW 550 kDa) containing balanced electrolytes (Na^+ 143 mmol litre^{-1}, Cl^- 124 mmol litre^{-1}, lactate 28 mmol litre^{-1}, Ca^{2+} 2.5 mmol litre^{-1}, K^+ 3 mmol litre^{-1}, Mg^{2+} 0.45 mmol litre^{-1}, glucose 5 mmol litre^{-1}).[11] This HES preparation impairs coagulation less than the standard HMW HES.[11] [12] We used activated thrombelastography (TEG) to assess the effects of volume replacement with Hextend® on measures of coagulation in patients undergoing major abdominal surgery, compared with another HES preparation (MW 130 kDa, DS 0.4) and RL.

Table 1 Patient details. Data are mean (SD) except for age [mean (range)] PRBC=packed red blood cells, FFP=fresh frozen plasma *$P<0.05$ compared with the other groups

	Hextend® (*n*=21)	**Ringer lactate** (*n*=21)	**HES 130/0.4** (*n*=21)
Age (yr)	62 (45–74)	61 (48–78)	60 (48–77)
Sex (F/M)	14/7	12/9	10/11
Height (cm)	171 (9)	174 (11)	173 (12)
Weight (kg)	74 (11)	76 (12)	72 (11)
ASA (II/III)	10/11	11/9	12/9
Duration of (min)			
Surgery	196 (78)	202 (62)	189 (70)
Anaesthesia	299 (79)	310 (63)	293 (62)
Type of surgery (number of patients)			
Colon	10	9	8
Gastrectomy	4	5	6
Whipple operation	2	2	1
Oesophagus	2	3	3
Pancreas resection	3	2	3
Allogeneic blood/blood products			
PRBC			
Number of patients	8	6	5
Units/group	29*	18	16
FFP			
Number of patients	5	5	4
Units/group	27*	16	14
Catecholamines (number of patients)			
Epinephrine	2	2	1
Norepinephrine	1	–	–
Survivors			
7 days	All	All	All
30 days	All	All	All

Methods

Patients

After ethics approval and with informed consent, we included 63 consecutive patients undergoing elective major abdominal surgery for malignancy. We excluded patients with renal insufficiency (serum creatinine >150 µmol litre^{-1}; blood urea nitrogen >6 mmol litre^{-1}), liver dysfunction (aspartate aminotransferase >40 U litre^{-1}, alanine aminotransferase >40 U litre^{-1}), anaemia (haemoglobin <10 g dl^{-1}), preoperative coagulation abnormalities [platelet count <100 nl^{-1}; activated partial thromboplastin time (aPTT) >70 s; fibrinogen <2 g dl^{-1}; antithrombin III <40%], patients taking heparin, vitamin K antagonists, corticosteroids or cyclooxygenase inhibitors, and patients with severe cardiac insufficiency (NYHA class III–IV).

The patients were allocated prospectively to one of the following groups using a sealed envelope system: group I (*n*=21), volume therapy with Hextend® (BioTime, Berkeley, CA, USA); group II (*n*=21), volume therapy with RL (B. Braun, Melsungen, Germany: Na^+ 130 mmol litre^{-1}, K^+ 5.4 mmol litre^{-1}, Cl^- 112 mmol litre^{-1}, Ca^{2+} 1.8 mmol litre^{-1}, lactate 27 mmol litre^{-1}); group III (*n*=21), treatment with 6% HES 130/0.4 (Fresenius, Bad Homburg, Germany).

Volume replacement was started after induction of anaesthesia (after baseline data had been obtained) and continued for 48 h until the morning of the second postoperative day. Volume was infused to keep central venous pressure (CVP) between 8 and 12 mm Hg. Red blood cells were transfused when haemoglobin was <8 g dl^{-1}, and fresh frozen plasma was given if coagulation measures were abnormal (aPPT >60 s, prothrombin time <50%, fibrinogen <2 g litre^{-1}) and bleeding occurred. We gave RL 500 ml h^{-1} to all patients during surgery. Additional RL was given to replace fluid losses from sweating and gastric tubes and RL was used as a solvent for drugs. When mean arterial pressure (MAP) was <50 mm Hg despite adequate filling pressure volume (CVP >10 mm Hg), epinephrine was given. Norepinephrine was added if volume therapy and dopamine did not keep MAP >50 mm Hg.

Premedication consisted of oral midazolam 1 h before surgery. Epidural anaesthesia was used in all patients. General anaesthesia was induced with thiopental 5 mg kg^{-1} and fentanyl 3 µg kg^{-1} and neuromuscular block was achieved with vecuronium 0.1 mg kg^{-1}. Anaesthesia was maintained with fentanyl, desflurane and vecuronium, titrated according to the patients' needs. In all patients, mechanical ventilation was with 50% air in oxygen to keep arterial oxygen saturation >95% and end-expiratory carbon dioxide between 35 and 40 mm Hg. ECG, arterial blood pressure and CVP were monitored continuously. Fluid warmers and blankets were used during surgery to maintain body temperature.

Table 2 Fluid balance during the study period (input and output cumulative). Mean (SD). *$P<0$ 05 compared with the other groups

	After surgery	5 h	1st day	2nd day (total)
Volume input (ml, cumulative value)				
Ringer lactate (ml)				
Hextend®	3050 (830)	3850 (460)	6150 (510)	8150 (690)
Ringer lactate	7950 (950)	9070 (920)	14 150 (1150)*	18 750 (1890)*
HES 130/0.4	2480 (390)	3920 (390)	5950 (480)	8230 (550)
Colloid (ml)				
Hextend®	1370 (190)	1490 (250)	1800 (220)	1970 (310)
HES 130/0 4	1810 (320)	2150 (350)*	2430 (310)*	2590 (260)*
Urine output (ml)				
Hextend®	790 (240)	2050 (340)	3050 (230)	5680 (480)
Ringer lactate	1950 (340)*	4400 (410)*	7700 (370)*	11 450 (460)*
HES 130/0.4	610 (270)	1850 (280)	2990 (390)	5500 (370)
Blood loss (ml)				
Hextend®	990 (310)*	1290 (280*	1680 (270*	1890 (260)*
Ringer lactate	760 (320)	940 (330)	1210 (350)	1430 (330)
HES 130/0 4	680 (220)	910 (230)	1180 (250)	1370 (250)

Table 3 Cardiovascular measurements Mean (SD). MAP=mean arterial pressure, CVP=central venous pressure; HR=heart rate

	Baseline	After surgery	5 h	1st day	2nd day
MAP (mm Hg)					
Hextend®	81 (10)	90 (14)	88 (13)	79 (13)	91 (12)
Ringer lactate	84 (12)	89 (10)	87 (11)	81 (12)	93 (11)
HES 130/0 4	82 (10)	91 (11)	91 (9)	82 (9)	90 (10)
CVP (mm Hg)					
Hextend®	7 (3)	9 (3)	9 (3)	8 (2)	10 (4)
Ringer lactate	7 (3)	8 (2)	8 (2)	8 (3)	8 (2)
HES 130/0.4	6 (2)	9 (2)	10 (2)	9 (3)	9 (3)
HR (beats min^{-1})					
Hextend®	78 (8)	81 (9)	90 (12	78 (10)	84 (11)
Ringer lactate	75 (10)	85 (12)	88 (15)	80 (11)	86 (13)
HES 130/0 4	77 (9)	82 (10)	86 (14)	81 (12)	84 (10)

After surgery, mechanical ventilation was continued as necessary until the patient was ready for tracheal extubation (stable circulation, spontaneous breathing with adequate blood gases and oesophageal temperature >36°C). The patients were managed by anaesthetists who were not involved in the study and were masked to the volume therapy.

Coagulation measurements

Standard coagulation variables [antithrombin III (AT III), fibrinogen, platelet count, aPTT] were measured from arterial blood samples using routine laboratory methods. Another 5 ml of citrated blood was taken for activated TEG using a four-channel TEG analyser (roTEG™; Nobis Diagnostics, Endingen, Germany). This modification of the conventional TEG system uses a different transducer that makes it less susceptible to mechanical stress, movement and vibration.[13] [14] The method is based on optical detection of the movement of a disposable plastic sensor attached to a short axle mounted on a ball-bearing. The sensor is inserted into the clotting blood. TEG monitoring provides continuous assessment of clot firmness, to measure the onset of coagulation [coagulation time (CT); standard TEG: reaction time (r)], the kinetics of clot formation [clot formation time (CFT); standard TEG: coagulation time (k)] and maximum clot firmness (MCF) (standard TEG: maximal amplitude (MA)].

TEG measurements were made within 10 min after blood sampling using a semiautomatic pipetting system after adding different activators to the blood sample (activated TEG). To assess intrinsic TEG (InTEG), clot formation was measured after recalcification of 300 µl of whole blood with 20 µl of 0.2 M calcium chloride and adding a surface activator (partial thromboplastin from rabbit brain; 20 µl). To assess extrinsic TEG (ExTEG), clot formation was measured after adding tissue thromboplastin (rabbit brain extract). To assess aprotinin TEG (ApTEG), ExTEG was measured in the presence of inhibition of fibrinolytic activity by aprotinin (aprotinin solution equivalent to 10 000 kallikrein inhibitor units ml^{-1}). Comparison of this result with the ExTEG value gives a measure of fibrinolytic activity.

All measurements were made by the same person. Measurements were made after induction of anaesthesia and before surgery, immediately after surgery, 5 h after surgery and on the mornings of the first and second days after surgery. The patient outcomes were followed-up for 30 days after surgery.

Statistics

A power analysis was done before the study started to determine the necessary number of patients in each group. The data used were from a previous TEG study on the effects of HES 130/0.4.[15] A 50% increase in reaction time (r) after treatment was taken to be the minimum clinically important difference we wished to detect. For an alpha error of 0.05 (two-sided) and type II error of 0.2, a total of 21

Table 4 Standard coagulation values. Mean (SD). *$P<0.05$ compared with the other groups. aPTT=activated partial thromboplastin time, AT III=antithrombin III

	Baseline	**After surgery**	**5 h**	**1st day**	**2nd day**
Haemoglobin (g dl^{-1})					
Hextend®	13.1 (1.0)	9.9 (1.0)	10.4 (1.0)	10.4 (0.5)	10.2 (0.8)
Ringer lactate	12.9 (1.0)	10.9 (1.0)	11.2 (0.9)	10.8 (0.8)	10.4 (0.8)
HES 130/0.4	12.7 (1.2)	10.4 (1.0)	10.8 (0.5)	10.9 (0.9)	10.7 (0.5)
Platelet count (nl^{-1})					
Hextend®	310 (42)	212 (58)	213 (43)	212 (34)	201 (45)
Ringer lactate	321 (59)	216 (47)	201 (57)	206 (38)	190 (44)
HES 130/0.4	299 (50)	222 (51)	198 (44)	201 (51)	212 (33)
aPTT (normal range 25–40 s)					
Hextend®	32 (3)	38 (3)	39 (5)	41 (4)	41 (3)
Ringer lactate	31 (3)	32 (4)	34 (4)	38 (5)	41 (4)
HES 130/0.4	31 (2)	34 (3)	35 (3)	39 (4)	39 (3)
Fibrinogen (normal range 200–500 mg dl^{-1})					
Hextend®	414 (76)	244 (61)	259 (54)	316 (71)	472 (79)
Ringer lactate	448 (88)	267 (76)	290 (73)	305 (65)	580 (68)*
HES 130/0.4	454 (88)	255 (59)	288 (55)	302 (64)	466 (55)
AT III (normal range 80–100%)					
Hextend®	85 (9)	62 (11)	66 (10)	58 (10)*	67 (11)
Ringer lactate	80 (10)	68 (10)	71 (11)	79 (11)	76 (10)
HES 130/0.4	81 (11)	60 (12)	69 (13)	73 (9)	74 (11)

patients per group was found to be necessary. Data are presented as mean (SD) unless otherwise indicated. Statistical analysis was done with software package SPSS/PC+ (version 4.0 SPSS, Chicago, IL, USA). Fisher's exact test was used for categorical data. A non-parametric test (Wilcoxon rank sum test) was used for variables that were not normally distributed (detected with the Kolmogorov–Smirnov test; e.g. use of blood products). Continuous, normally distributed data were compared using paired and unpaired Student's *t*-test or analysis of variance for repeated measures (ANOVA, followed by Scheffé's test). Bonferroni correction was applied when multiple comparisons were made. Continuous, non-normally distributed data were compared using the Wilcoxon test. Correlation analysis was used to correlate blood loss and data from TEG. $P<0.05$ was considered significant.

Results

Patient details and the type of surgery are given in Table 1. There were no obvious differences between the groups. Significantly more blood and blood products were given to the Hextend®-treated patients than to the two other groups (Table 1). Significantly more HES 130/0.4 [2590 (260) ml] than Hextend® [1970 (310) ml] was given in the study period (Table 2). Blood loss was greatest in the Hextend® group, but did not differ between RL- and HES 130/0.4-treated patients (Table 2). There was no significant correlation between blood loss and TEG measurements. Cardiovascular measurements and haemoglobin changes were similar in all groups (Tables 3 and 4). Standard coagulation tests showed no significant differences between the groups, except for small differences in fibrinogen (RL, significant difference) and AT III concentrations on the first and second days (Table 4).

TEG data were similar and within the normal range in all three groups at baseline (Figs 1–3). Using ExTEG and InTEG, CT and CFT were prolonged most in the Hextend®-treated patients and were greater than in the two other groups immediately after surgery, 5 h after surgery and on the first day (Figs 1 and 2). On the second day, CT and CFT in the Hextend® group were still greater than baseline but were not different from values for the other two groups. Changes in ExTEG-MCF/ApTEG-MCF were significantly more pronounced in the Hextend® patients than in the other two groups, indicating more fibrinolysis (Figs 1 and 3).

Volume therapy with RL caused shortening of the CT (ExTEG, InTEG) at the end of surgery and 5 h after surgery (Figs 1 and 2), indicating moderate hypercoagulability. This returned to normal later in the study period (first and second days) (Figs 1 and 2).

Discussion

The use of HES as a plasma substitute is sometimes restricted primarily because of reports of altered coagulation.[2 3 8] HMW HES and highly substituted hydroxyethyl starch preparations can impair blood clotting and increase postoperative bleeding.[8 16] A modified HMW HES (Hextend®) and a new LMW/low-substituted HES (6% HES 130/0.4) have been developed to prevent these adverse effects.

We used TEG to assess the effects of the different plasma substitutes, as measuring plasma concentrations of coagulation proteins and other markers of coagulation appears to be a very simplistic approach for complete assessment of the complex changes that can occur in haemostasis.[17] TEG

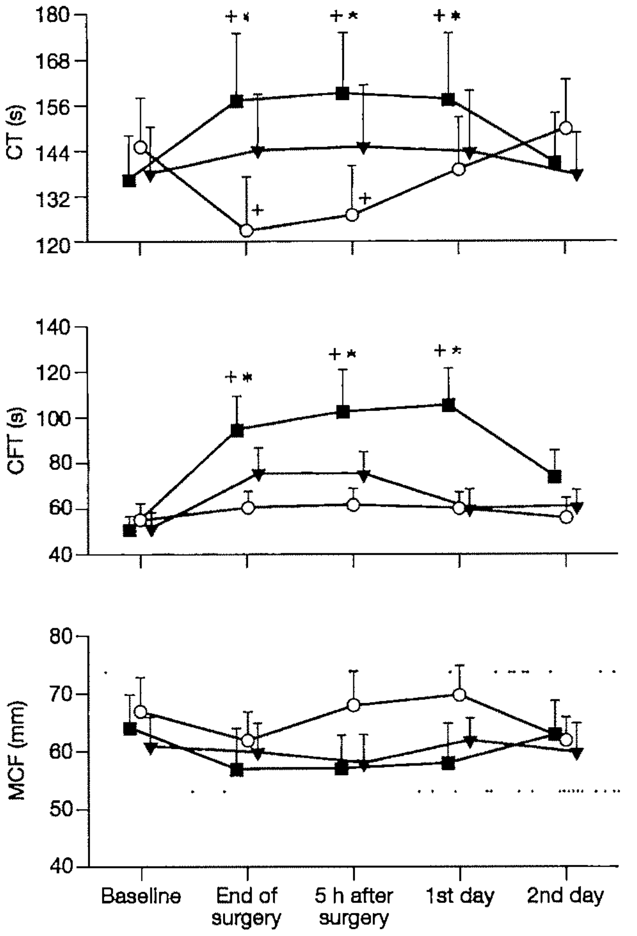


Fig 1 Mean (SD) coagulation time [CT (onset of coagulation); normally <50 s, standard TEG: reaction time (r)], clot formation time [CFT (kinetics of clot formation), normally <180 s; standard TEG: coagulation time (k)], and maximum clot firmness [MCF, normally 53–74 mm, standard TEG. maximum amplitude (MA)] using (extrinsic) activation by tissue thromboplastin (extrinsic TEG). $^*P<0.05$ compared with the other groups †$P<0.05$ compared with baseline data. Filled squares, Hextend®; filled triangles, HES 130/0.4; open circles, Ringer lactate. Horizontal dotted lines show the normal range.

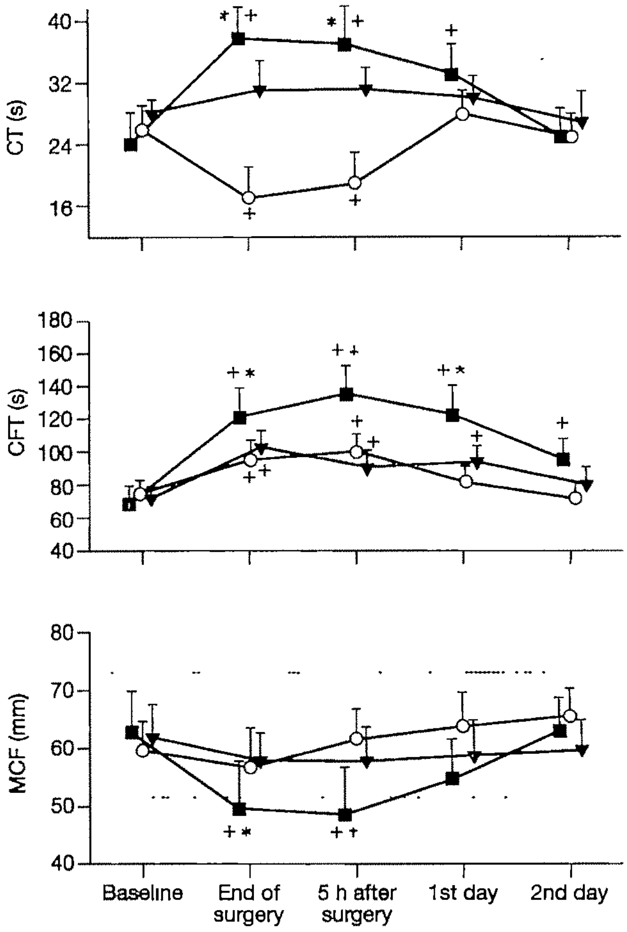


Fig 2 Mean (SD) coagulation time [CT (onset of coagulation); normally <160 s], clot formation time (CFT, kinetics of clot formation, normally <180 s) and maximum clot firmness (MCF, normally 53–74 mm) using activation by surface activator [activation of the intrinsic system (intrinsic TEG)]. $^*P<0.05$ compared with the other groups. †$P<0.05$ compared with baseline data. Symbols as in Fig 1. Horizontal dotted lines show the normal range.

appears to be a more complete means of following the dynamic process of coagulation compared with conventional tests of haemostasis.[18] [19] TEG monitors the kinetics of the complete haemostatic process, whereas with plasma coagulation tests only the speed of fibrin formation is assessed. TEG examines the interplay of the protein coagulation cascade, fibrinogen, and platelet function. TEG measurements can assist management of coagulation during and after surgery, and reduce blood loss and use of blood and blood products.[18] [20] [21] We used modified, activated TEG instead of conventional ('non-activated') TEG because different features of the coagulation process can be detected sooner and better by activated TEG.[22] [23]

We found that Hextend® had the most adverse effects on activated TEG monitoring, whereas HES with a low MW and low DS affected coagulation less and RL caused a small increase in coagulation. Our results contradict other *in vitro* and *in vivo* studies, which did not show that Hextend® had adverse effects on coagulation, except those expected as a result of haemodilution.[11] [12] An *in vitro* study with different dilutions of plasma with Hextend® (up to 25% plasma/75% Hextend®) found no adverse effect on coagulation,[12] with possibly a protective effect on factors sensitive to prothrombin time (I, II, VII, X), on functional fibrinogen, and on factors of factor VIII macromolecular complex components (FVIII:C, VIII:vWF, VIII:vWF multimers), and no evidence of disseminated intravascular coagulation or procoagulant activation. The value of *in vitro* coagulation studies is not clear, because in such studies the effects of surgery on the coagulation process are absent. Even after minor surgery (mammoplasty), a hypercoagulable state was seen, whereas after complex, lengthy surgery hypocoagulability may also be present.[24]

HMW HES (hetastarch) can affect coagulation by adverse effects on both von Willebrand factor and platelet aggregation.[8] Most reports of impaired haemostasis with

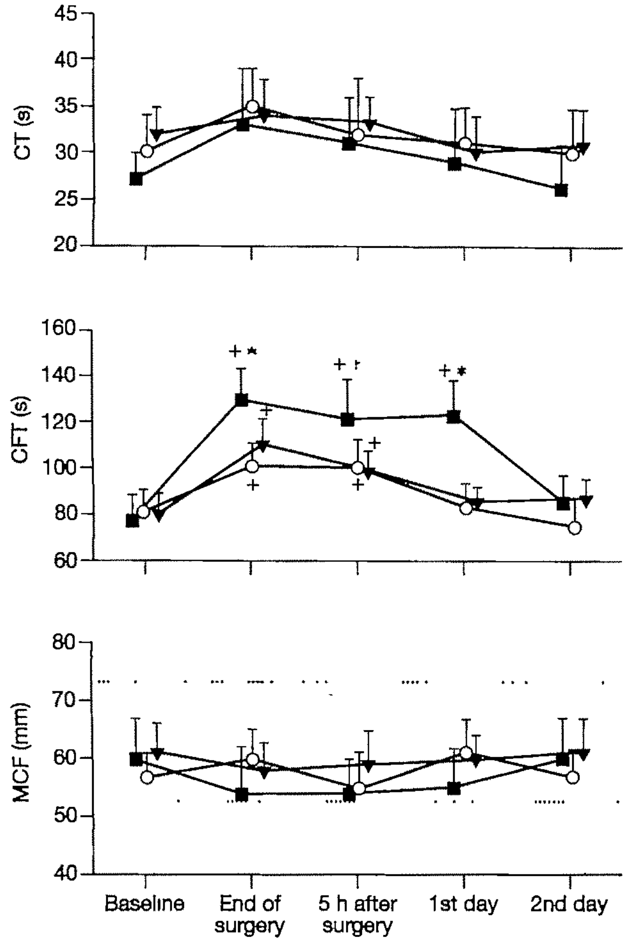


Fig 3 Mean (SD) coagulation time (CT; onset of coagulation, normally <50 s), clot formation time (CFT; kinetics of clot formation, normally <180 s) and maximum clot firmness (MCF; normally 53–74 mm) after extrinsic activation and *in vitro* inhibition of fibrinolytic activity with aprotinin (aprotinin TEG). $^*P<0.05$ compared with the other groups $^\dagger P<0.05$ compared with baseline data. Symbols as in Fig. 1. Horizontal dotted lines show the normal range

HES are associated with this first-generation HMW HES.[2 8] A study of patients undergoing major surgery compared Hextend® with standard HMW HES (hetastarch), and found no differences in perioperative blood transfusion and estimated blood loss.[11] Onset of clot formation (r – CT) was slower in the patients treated with hetastarch compared with those given Hextend®, and other TEG variables showed no differences between the two groups. Why the modified, 'balanced' Hextend® solution is almost free of this side-effect on coagulation is not clear. The authors speculated that the addition of Ca^{2+}, lactated buffer and physiological concentrations of glucose and lower Cl^- concentrations gave Hextend® a favourable side-effect profile.[11] Our study using TEG monitoring in patients found no benefit of Hextend® administration either in onset of coagulation (r – CT)] or in the kinetics of clot formation (k – CFT). The difference of ExTEG MCF and ApTEG MCF (TEG measured in the presence of an inhibitor of fibrinolysis) showed reduced MCF [standard TEG: maximal amplitude (MA)] with Hextend® compared with the new HES 130/0.4.

The shorter coagulation time in our RL-treated patients supports previous studies. In *in vitro* and *in vivo* TEG studies, Ruttman and colleagues[25 26] showed that haemodilution *per se* increased the coagulability of whole blood (decrease in r and k; increase in MA) most likely due to induction of thrombin formation. This hypercoagulability was greater in saline- than in gelatin-diluted samples. In an *in vitro* TEG study,[27] only extreme haemodilution with RL (10:10) increased the k and MA values, whereas the r value remained unchanged. Ng and Lo[28] also reported increased coagulability when surgical blood loss was replaced with crystalloids. Monkhouse[29] showed that diluting plasma with saline increases the thrombin activity two- to three-fold. This increase in thrombin activity in diluted samples was assumed to result from decreased antithrombin action rather than any real increase in thrombin generation. Similar changes in thrombin generation occur *in vivo* after giving large amounts of saline solution for acute haemorrhage.[29] This crystalloid-induced increase in coagulability could predispose patients to deep vein thrombosis.[30]

The new LMW low-substituted HES (HES 130/0.4) has better physicochemical properties compared with other HES solutions[31] and its effect on coagulation also appears to be favourable. Konrad and colleagues[32] used an *in vitro* haemodilution model and SONOCLOT analysis to measure the effects of this HES preparation on haemostasis: HES 130/0.4 affected clot maturation significantly less than other HES preparations and it had less effect on other aspects of clot formation and retraction. Clinical studies with HES 130/0.4 in orthopaedic[10] and cardiac patients[9] reported beneficial effects on bleeding tendency and the use of blood and blood products.

In summary, modification of an HMW starch did not eliminate adverse effects on coagulation when assessed by activated TEG. Reducing the molecular weight and the degree of substitution (HES 130/0.4) caused less impairment of haemostasis. Volume replacement only with crystalloids (RL) in patients undergoing major abdominal surgery was associated with moderate, short-lasting hypercoagulability.

References

1 Mythen MG, Webb AR. Intra-operative gut mucosal hypoperfusion is associated with increased post-operative complications and costs. *Intensive Care Med* 1994; **20**: 99–104

2 Warren BB, Durieux ME. Hydroxyethylstarch: safe or not? *Anesth Analg* 1997; **84**: 206–12

3 Cope JT, Banks D, Mauney MC, *et al.* Intraoperative hetastarch infusion impairs hemostasis after cardiac surgery operations. *Ann Thorac Surg* 1997; **63**: 78–82

4 Baldassare S, Vincent JL. Coagulopathy induced by hydroxyethyl starch. *Anesth Analg* 1997; **84**: 451–3

5 Traylor RJ, Pearl RG. Crystalloid versus colloid versus colloid: all colloids are not created equal. *Anesth Analg* 1996; **83**: 209–12

6 Strauss RG. Volume replacement and coagulation: a comparative review. *J Cardiothorac Anesth* 1988; **2** (Suppl 1): 24–32

7 Boldt J, Muller M, Heesen M, Heyn O, Hempelmann G. Influence of different volume therapies on platelet function in the critically ill. *Intensive Care Med* 1996; **22**: 1075–81

8 deJonge E, Levi M. Effects of different plasma substitutes on blood coagulation: a comparative review. *Crit Care Med* 2001; **29**: 1261–7

9 Huet RCGG, Siemons AW, Baus D, *et al.* A novel hydroxyethyl starch (Voluven®) for effective perioperative plasma volume substitution in cardiac surgery. *Can J Anesth* 2000; **47**: 1207–15

10 Langeron O, Doelberg M, Ang ET, Bonnet F, Capdevila X, Coriat P. Voluven®, a lower substituted novel hydroxyethyl starch (HES 130/0.4), causes fewer effects on coagulation in major orthopedic surgery than HES 200/0.5. *Anesth Analg* 2001; **92**: 855–62

11 Gan TJ, Bennett-Guerrero E, Phillips-Bute B, *et al.* Hextend®®, a physiologically balanced plasma expander for large volume use in major surgery: a randomized phase III clinical trial. *Anesth Analg* 1999; **88**: 992–8

12 Bick RL. Evaluation of a new hydroxyethyl starch preparation (Hextend®) on selected coagulation parameters. *Clin Appl Thrombosis/Hemostasis* 1995; **1**: 215–29

13 Mahla E, Lag T, Vicenzi M, *et al* Thrombelastography for monitoring prolonged hypercoagulability after major abdominal surgery. *Anesth Analg* 2001; **92**: 572–7

14 Calatzis A, Haas S, Godje O. Thrombelastographic coagulation monitoring during cardiovascular surgery with the RoTEG coagulation analyzer. In: Pifarré R, ed. *Management of Bleeding in Cardiovascular Surgery*. Philadelphia: Hanley & Belfus, 2000; 215–26

15 Jamnicki M, Zollinger A, Seifert B, et al. Compromised blood coagulation: An *in vitro* comparison of hydroxyethyl starch 130/0.4 and hydroxyethyl starch 200/0.5 using thrombelastography. *Anesth Analg* 1998; **87**: 989–93

16 Treib J, Haass A, Pindur G, *et al.* All medium starches are not the same: influence of hydroxyethyl substitution of hydroxyethyl starch on plasma volume, hemorrheologic conditions, and coagulation. *Transfusion* 1996; **36**: 450–5

17 Spiess BD. Maintenance of homeostasis in coagulation during cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 1999; **13**: 2–5

18 Pivalizza EG. Thrombelastography: another point of view. *Anesth Analg* 2001; **93**: 517–8

19 Entholzner EK, Mielke LL, Calatzis AN, Feyh J, Hipp R, Hargasser SR. Coagulation effects of a recently developed hydroxy-ethyl starch (HES 130/0.4) compared to hydroxyethyl starches with higher molecular weight. *Acta Anaesthesiol Scand* 2000; **44**: 1116–21

20 Dietrich GV, Schueck R, Menges T, Kiesenbauer NP, Fruehauf AC, Marquardt I. Comparison of four methods for the determination of platelet function in whole blood in cardiac surgery. *Thromb Res* 1998; **89**: 295–301

21 Shore-Lesserson L, Manspeizer HE, DePerio M, Francis S, Vela-Cantos F, Ergin A. Thrombelastography-guided transfusion algorithm reduces transfusions in complex cardiac surgery. *Anesth Analg* 1999; **88**: 312–9

22 Miller BE, Guzzetta NA, Tosone SR, Levy JH. Rapid evaluation of coagulopathies after cardiopulmonary bypass in children using modified thrombelastography. *Anesth Analg* 2000; **90**: 1324–30

23 Tuman KJ, McCarthy RJ, Djuric M, *et al.* Evaluation of coagulation during cardiopulmonary bypass with a heparinase-modified thrombelastography assay. *J Cardiothorac Vasc Anesth* 1994; **8**: 144–9

24 Payen JF, Baruch M, Horvilleur E, *et al.* Changes in specific markers of haemostasis during reduction mammoplasty. *Br J Anaesth* 1998; **80**: 464–6

25 Ruttmann TG, James MFM, Viljoen JF. Haemodilution induces a hypercoagulable state. *Br J Anaesth* 1996; **76**: 412–4

26 Ruttmann TG, James MFM, Aronson I. *In vivo* investigation into the effects of haemodilution with hydroxyethyl starch (200/0.5) and normal saline on coagulation. *Br J Anaesth* 1998; **80**: 612–6

27 Petroianu GA, Liu J, Maleck WH, Mattinger C, Bergler WF. The effect on *in vitro* hemodilution with gelatin, dextran, hydroxyethylstarch, or Ringer's solution on thrombelastograph. *Anesth Analg* 2000; **90**: 795–800

28 Ng KFJ, Lo JWR. The development of hypercoagulability state, as measured by thrombelastography, associated with intraoperative surgical blood. *Anaesth Intens Care* 1996; **24**: 20–5

29 Monkhouse FC. Relationship between antithrombin and thrombin levels in plasma and serum. *Am J Physiol* 1959; **197**: 984–8

30 Janvrin SB, Davies G, Greenhalgh RM. Postoperative deep vein thrombosis caused by intravenous fluids during surgery. *Br J Surg* 1980; **67**: 690–3

31 Waitzinger J, Bepperling F, Pabst G, Opitz J, Muller M, Baron JF. Pharmacokinetics and tolerability of a new hydroxyethylstarch (HES) specification (HES 130/0.4) after single-dose infusion of 6% or 10% solution in healthy volunteers. *Clin Drug Invest* 1998; **16**: 151–60

32 Konrad CH, Markl T, Schuepfer G, Gerber H, Tschopp M. *In vitro* effects of different medium molecular hydroxyethylstarch solutions and lactated Ringer's solution on coagulation using SONOCLOT. *Anesth Analg* 2000; **90**: 274–9

British Journal of Anaesthesia **89** (**5**): 729–32 (2002)

The laryngeal tube compared with the laryngeal mask: insertion, gas leak pressure and gastric insufflation

T. Asai[1*], A. Kawashima[2], I. Hidaka[2] and S. Kawachi[2]

[1]Department of Anaesthesiology, Kansai Medical University, 10-15 Fumizono-cho, Moriguchi City, Osaka 570-8507, Japan. [2]Department of Anaesthesia, Matsue Red Cross Hospital, Matsue City, Shimane 690-8506, Japan

**Corresponding author*

Background. We have compared the laryngeal tube and laryngeal mask in 22 patients for the success rate of insertion, gas leak pressure and the incidence of gastric insufflation.

Method. In a randomized, crossover design, the laryngeal tube and laryngeal mask were inserted in turn after induction of anaesthesia and neuromuscular block. The cuffs were inflated until the intracuff pressure reached 60 cm H_2O. We measured adequacy of ventilation and the minimum airway pressure at which gas leaked around the cuff. The presence or absence of gastric insufflation was studied at an inflation pressure of 20 cm H_2O.

Results. It was possible to ventilate through the laryngeal tube in 21 patients and through the laryngeal mask in 21 patients. The mean leak pressure for the laryngeal tube (26 (SD 5) cm H_2O) was significantly greater than that for the laryngeal mask (19 (4) cm H_2O) ($P<0.01$; 95% confidence intervals for mean difference: 5.3–10.2 cm H_2O). Gastric insufflation did not occur when the laryngeal tube was used and was noted in three patients when the laryngeal mask was used.

Conclusion. The laryngeal tube provides a better seal in the oropharynx than the laryngeal mask.

Br J Anaesth 2002; **89**: 729–32

Keywords: equipment, masks laryngeal; equipment, tubes laryngeal

Accepted for publication: May 12, 2002

The laryngeal tube (VBM, Medizintechnik, Germany) (Fig. 1) has been developed to secure a patent airway during spontaneous breathing or controlled ventilation. It consists of an airway tube with a small cuff attached at the tip (distal cuff) and a larger cuff in the middle of the tube (proximal cuff). The cuffs are inflated through a single pilot tube and balloon, through which the cuff pressure can be monitored. There is a standard 15-mm connector on the proximal end of the device so that it can be attached to a breathing system. The device is made of silicone and is re-usable after sterilization in an autoclave. Six sizes are available, suitable for neonates to large adults. When the device is inserted, it lies along the length of the tongue, and the distal tip is positioned in the hypopharynx (Fig. 2). The proximal cuff provides a seal by forming a plug in the upper pharynx and the distal cuff seals the oesophageal inlet. There is a distal aperture in the tube between the two cuffs. Three black lines on the tube near the connector indicate adequate depth of insertion when aligned with the teeth.

The laryngeal tube is now commercially available, but there have been only two clinical studies,[1 2] neither of which compared the efficacy of the laryngeal tube with other airway devices. The main aim of this study was to compare the laryngeal tube with the laryngeal mask airway (LMA)[†] in terms of the success of insertion, gas leak pressure and the incidence of gastric insufflation.

Patients and methods

After obtaining approval from the institutional Research Ethics Committee and written informed consent, we studied 22 patients (ASA I or II, aged 18–78 yr, height 148–180 cm, weight 45–81 kg) undergoing elective surgery. Patients with any abnormality of the neck, upper respiratory tract or upper alimentary tract, or at risk of regurgitation of gastric

---

[†] LMA® is the property of Intavent Limited.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

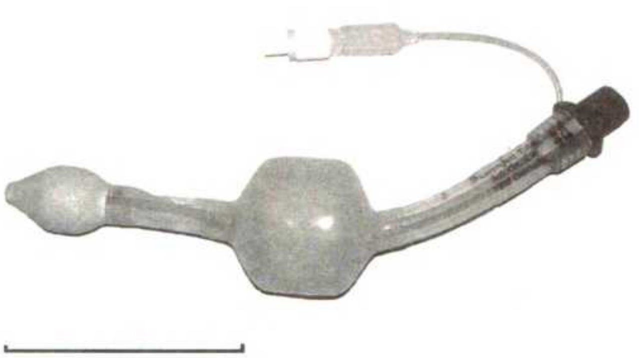


Fig 1 The laryngeal tube (VBM, Germany). The black lines on the tube near the connector indicate adequate depth of insertion when aligned with the teeth. The line indicates a distance of 10 cm.

contents were excluded. Patients with Mallampati class 3 or 4[3 4] were also excluded.

In the anaesthetic room, an electrocardiograph, a pulse oximeter and an arterial pressure cuff were attached and an i.v. cannula was inserted. A firm pad (7 cm in height) was placed under the patient's occiput. After the patient had breathed oxygen through a facemask for a minimum of 3 min, anaesthesia was induced with a sleep dose of propofol 2.0–3.0 mg kg^{-1} i.v., supplemented with fentanyl 2 μg kg^{-1}. Neuromuscular block was obtained with vecuronium and was confirmed using a peripheral nerve stimulator. Anaesthesia was maintained with a continuous infusion of propofol while the patient was breathing oxygen (but not nitrous oxide) until the end of the study.

In a randomized, crossover design, the laryngeal tube and laryngeal mask were inserted in turn. The order was randomized by tossing a coin. Three anaesthetists were involved in insertion of these devices. All of them had used the laryngeal mask routinely for between 2 and 12 yr. One anaesthetist had used the laryngeal tube more than 100 times, whereas the other two had used it fewer than 10 times before the start of the study.

The sizes of laryngeal tube[1] and laryngeal mask[5] according to the patient's height are shown in Table 1. The laryngeal tube was inserted into the oropharynx by the following method. Before insertion, the cuffs were deflated and a water-soluble lubricant (KY jelly) was applied to the cuffs. The patient's neck was extended ('sniffing position'). The tip of the laryngeal tube was placed against the hard palate behind the upper incisors and the device was slid down in the centre of the mouth until a resistance was felt or the second bold black line on the tube (Fig. 1) had just passed between the upper and lower teeth. The cuffs were inflated using a cuff inflator (VBM, Medizintechnik, Germany) until the intracuff pressure reached approximately 60 cm H_2O.[1] The laryngeal mask was inserted using the technique described in the manufacturer's instruction manual, and its cuff inflated using the cuff inflator until the intracuff pressure reached approximately 60 cm H_2O.[6]

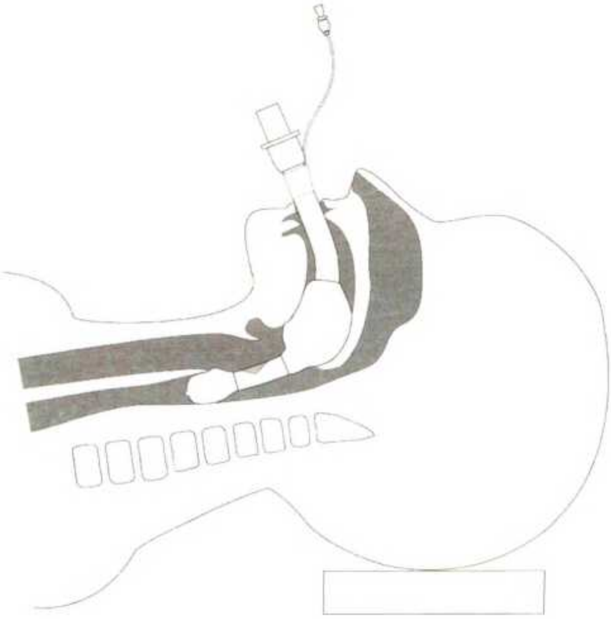


Fig 2 The laryngeal tube in place. When inserted, the device lies along the length of the tongue and the distal tip is positioned in the hypopharynx. The cuff is inflated until the intracuff pressure reaches 60 cm H_2O.

Table 1 Size of the laryngeal tube and the laryngeal mask used[1 5]

	Laryngeal tube	Laryngeal mask
Height ⩾155 cm		
Men	4	5
Women	4	4
Height <155 cm		
Men	3	4
Women	3	3

After insertion of the device being tested, we connected the breathing system and assessed adequacy of ventilation by gently squeezing the reservoir bag and observing the presence of end-tidal carbon dioxide waveforms and chest movement. If it was not possible to ventilate the lungs, the position of the test device was adjusted by gently pushing or pulling it. Adequacy of ventilation was then re-assessed. If it was not possible to insert the device or ventilate through it, one more attempt at insertion of the device was allowed. If placement had failed after two attempts, the study was abandoned and the airway was maintained through either a facemask or a tracheal tube.

If ventilation was possible, the device was fixed to the patient by the following methods: for the laryngeal tube, the bite block provided was inserted, the laryngeal tube snagged into its wedge and both were fixed using sticky tape (Fig. 1). For the laryngeal mask, a wad of gauze was inserted into the patient's mouth and both were fixed using sticky tape. After fixation of the device, the airway pressure was initially maintained at 18 cm H_2O by squeezing the reservoir bag for

Table 2 Adequacy of ventilation through the laryngeal tube and the laryngeal mask. Data are number of patients (%)

Category	Airway pressure at which gas leak occurred	Laryngeal tube	Laryngeal mask
Excellent	No gas leak at 30 cm H_2O	12 (55)	0 (0)
Good	18–28 cm H_2O	8 (36)	15 (68)
Fair	10–16 cm H_2O	1 (5)	6 (27)
Poor	8 cm H_2O or less	0 (0)	0 (0)
Failure	Failed insertion or failed ventilation	1 (5)	1 (5)

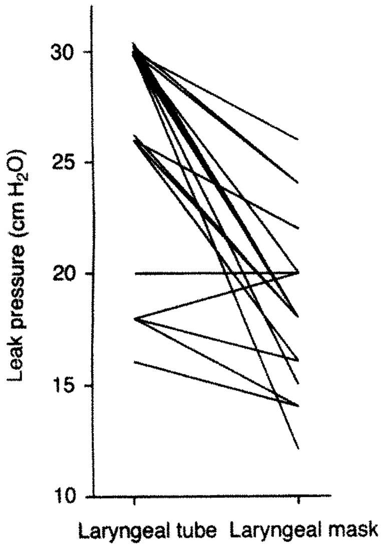


Fig 3 The minimum airway pressure at which gas leaked around the cuff of the test device. Symbols are displaced slightly on the *Y* axis if they are the same values. Lines join measurements with the two devices in the same subject.

3 s. The inflation pressure was measured using an airway pressure gauge. If there was no gas leak, airway pressure was increased at each breath by 2 cm H_2O, whereas if there was gas leak, airway pressure was decreased at each breath by 2 cm H_2O. The airway pressure at which gas leaked around the test device was recorded. The adequacy of ventilation was scored in the five categories shown in Table 2.

The presence or absence of gastric insufflation was then studied at the inflation pressure of 20 cm H_2O by auscultation over the epigastrium. It has been shown that a volume of gas, as little as 5 ml, entering the stomach from the oesophagus can be detected.[7 8] The cuff of the test device was then deflated and the device removed. The volume of air withdrawn from the cuff was recorded.

Our main interest was to compare the leak pressures between the laryngeal tube and laryngeal mask, and thus the number of patients required was calculated on the basis of this factor. The mean airway pressure at which gas leaks around the laryngeal mask has been reported to range from 18 to 20 cm H_2O (SD approximately 5 cm H_2O).[9] We considered that an increase in the leak pressure to 25–26 cm H_2O (i.e. a 30% increase) would be a clinically important difference. Twenty-two patients would be required to detect this difference with a power of 80% (if comparison was made between two independent groups). For gastric insufflation, we did not plan to apply any hypothesis for comparing the groups, since the number of patients we planned to study could be too small to detect a difference, and because the clinical significance of this observation during such a short period of time at a fixed airway pressure (20 cm H_2O) was not certain.

Plots of normal scores showed that the data for the differences in the leak pressures between the laryngeal tube and laryngeal mask were normally distributed, and thus a paired *t*-test was used for comparison. $P<0.05$ was considered significant. The 95% confidence intervals (CI) for the difference in the mean leak pressure between the laryngeal tube and the laryngeal mask were also calculated.

Results

We studied nine women (four at least 155 cm tall and five less than 155 cm tall) and 13 men (all at least 155 cm tall).

It was possible to insert and ventilate through the laryngeal tube in 21 of 22 patients (without changing its position after inflation of the cuffs). Ventilation was adequate at the first attempt in 19 patients and at the second attempt in another two patients. Adequate ventilation was not possible after two attempts in the remaining one patient. It was possible to insert and ventilate through the laryngeal mask in 21 of 22 patients. Ventilation was adequate at the first attempt in 20 patients and at the second attempt in another one patient. Adequate ventilation was not possible in the remaining one patient.

The mean volume of air placed in the cuff to give the intracuff pressure of 60 cm H_2O was 75 (SD 8) ml for the laryngeal tube and 19 (4) ml for the laryngeal mask. The minimum mean airway pressure at which gas leaked around the cuff of the laryngeal tube was 26 (5) cm H_2O, which was significantly greater than that of the laryngeal mask (19 (4) cm H_2O) ($P<0.01$; 95% CI for mean difference: 5.3–10.2 cm H_2O) (Fig. 3). When the laryngeal tube was used, gas did not leak around the cuff at an airway pressure of 30 cm H_2O in 12 of 22 patients (55%), whereas when the laryngeal mask was used gas always leaked around the cuff with an airway pressure of less than 30 cm H_2O (Table 2).

Gastric insufflation did not occur in any patient when the laryngeal tube was used, and was noted in three of 22 patients when the laryngeal mask was used.

Discussion

The success rate of obtaining a patent airway through the laryngeal tube was high (95%). This result is consistent with previous reports, in which success rate was 94–100%.[1 2] We also found that the laryngeal tube provided a patent airway as frequently as the laryngeal mask.

The laryngeal tube provided a good airtight seal in most patients (Table 2), and often there was no gas leak around the cuff at an airway pressure of 30 cm H_2O. The leak pressure for the laryngeal tube was significantly higher than that for the laryngeal mask (Fig. 3).

Compared with the laryngeal mask, the laryngeal tube provided a significantly better seal to the oropharynx. In addition, gastric insufflation did not occur in any of 22 patients when the laryngeal tube was used, whereas it occurred in three patients when the laryngeal mask was used. Therefore, the laryngeal tube may be more suitable than the laryngeal mask during intermittent positive-pressure ventilation. However, studies of the laryngeal tube are few, with only a few preliminary reports[10–12] of its efficacy during the entire course of anaesthesia and of postoperative complications such as sore throat or lingual nerve palsy. Therefore, caution is required with the results obtained in this study until the safety of the routine use of the laryngeal tube during anaesthesia is known.

Acknowledgement

Japan Medico donated the laryngeal tubes for the study.

References

1 Asai T, Murao K, Shingu K. Efficacy of the laryngeal tube during intermittent positive pressure ventilation. *Anaesthesia* 2000; **55**: 1099–102

2 Dörge V, Ocker H, Wenzel V, Schmucker P. The laryngeal tube: a new simple airway device. *Anesth Analg* 2000; **90**: 1220–2

3 Mallampati SR, Gatt SP, Gugino LD, *et al.* A clinical sign to predict difficult tracheal intubation: a prospective study. *Can Anaesth Soc J* 1985; **32**: 429–34

4 Samsoon GLT, Young JRB. Difficult tracheal intubation: a retrospective study. *Anaesthesia* 1987; **42**: 487–90

5 Brimacombe JR, Brain AIJ, Berry AM. *The Laryngeal Mask Instruction Manual for Anaesthesia.* Henley-on-Thames, UK: Intavent Research Ltd, 1999

6 Asai T, Brimacombe J. Cuff volume and size selection with the laryngeal mask. *Anaesthesia* 2000; **55**: 1179–84

7 Asai T, Barclay K, McBeth C, Vaughan RS. Cricoid pressure applied after placement of the laryngeal mask prevents gastric insufflation but inhibits ventilation. *Br J Anaesth* 1996; **76**: 772–6

8 Brimacombe J, Keller C, Kurian S, Myles J. Reliability of epigastric auscultation to detect gastric insufflation. *Br J Anaesth* 2002; **88**: 127–9

9 Asai T, Morris S. The laryngeal mask airway: its features, effects and role. *Can J Anaesth* 1994; **41**: 930–60

10 Asai T, Kawashima A, Hidaka I, Kawachi S. Laryngeal tube: its use for controlled ventilation. *Masui* 2001; **50**: 1340–1

11 Agrò F, Galli B, Ravussin P. Preliminary results using the laryngeal tube for supraglottic ventilation. *Am J Emerg Med* 2002; **20**: 57–8

12 Miller DM, Youkhana I, Pearce AC. The laryngeal mask and VBM laryngeal tube compared during spontaneous ventilation. A pilot study. *Eur J Anaesthesiol* 2001; **18**: 593–8

British Journal of Anaesthesia **89** (**5**): 733–8 (2002)

Fibreoptic tracheal intubation after placement of the laryngeal tube[†]

H. V. Genzwuerker[1]*, T. Vollmer[2] and K. Ellinger[1]

[1]*Department of Anaesthesiology and Intensive Care Medicine, University Hospital Mannheim, Theodor-Kutzer-Ufer 1–3, D-68167 Mannheim, Germany.* [2]*Department of Internal Medicine, Fuerst-Stirum-Hospital at Bruchsal, Gutleutstrasse 1–14, D-76646 Bruchsal, Germany*

**Corresponding author*

Background. The laryngeal tube is a new alternative for securing the airway. After adequate oxygenation, insertion of a tracheal tube is still required in many situations. In such circumstances, fibreoptic placement of a tube exchange catheter after placement of the laryngeal tube is possible before tracheal intubation. Throughout the procedure, oxygen administration can continue via the laryngeal tube, the tube exchange catheter and the tracheal tube.

Methods. The feasibility of this technique was tested in 10 patients scheduled for elective surgery.

Results. The laryngeal tube was placed at the first attempt with adequate ventilation in all patients. The tube exchange manoeuvre was performed successfully in all but one patient.

Conclusion. This technique is an important alternative for airway management and provides a significant degree of patient safety.

Br J Anaesth 2002; **89**: 733–8

Keywords: airway, difficult; equipment, catheters tube exchange; equipment, tubes laryngeal; intubation tracheal, technique

Accepted for publication: June 18, 2002

Establishing a patent airway is the primary aim during general anaesthesia as well as in emergency situations. While tracheal intubation is considered the gold standard, it requires adequate skill to secure the airway. The reported incidence of difficult intubation ranges from 0.05 to 18%.[1]

The American Society of Anesthesiologists Task Force on Management of the Difficult Airway points to the importance of alternative, less invasive devices to allow adequate oxygenation when tracheal intubation fails.[2] A new alternative is the laryngeal tube (VBM Medizintechnik, Sulz am Neckar, Germany), which was introduced to the European market in 1999.[3] First reports of successful use of the laryngeal tube in out-of-hospital emergency airway management suggest that this device might provide a feasible alternative to tracheal intubation.[4 5] The laryngeal tube is a single-lumen tube with an oesophageal and a pharyngeal cuff that are connected to a single inflation line with a ventral opening for ventilation between the two cuffs (Fig. 1).[6] After blind insertion, the device provides a patent airway in the majority of patients at the first attempt.[7 8] The laryngeal tube can be inserted quickly without extensive training and is considered a simple tool for airway management.[9] The oesophageal cuff of the laryngeal tube also allows a good airway seal,[7] which was found to be significantly better than that of the standard laryngeal mask airway.[10] In emergency situations and in some elective procedures (e.g. positioning in the prone position), tracheal intubation would still be required to protect the patient from aspiration.[11 12]

Oxygenation of the patient can be achieved by inserting a laryngeal tube, but when replacement by a tracheal tube is necessary, maximum patient safety must be sought. This can be achieved when oxygen can be provided throughout the tube exchange process. The object of this study was to assess the efficacy of a technique using a tube exchange catheter, which has been described for other devices[13 14] but not for the laryngeal tube. The laryngeal tube might be considered a dedicated airway; it is defined as 'an upper airway device dedicated to the maintenance of airway

---

[†] Results were presented in part as a poster at the Austrian International Congress 2001 and the R. Kucher Forum, Vienna, Austria, 12–14 September 2001.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

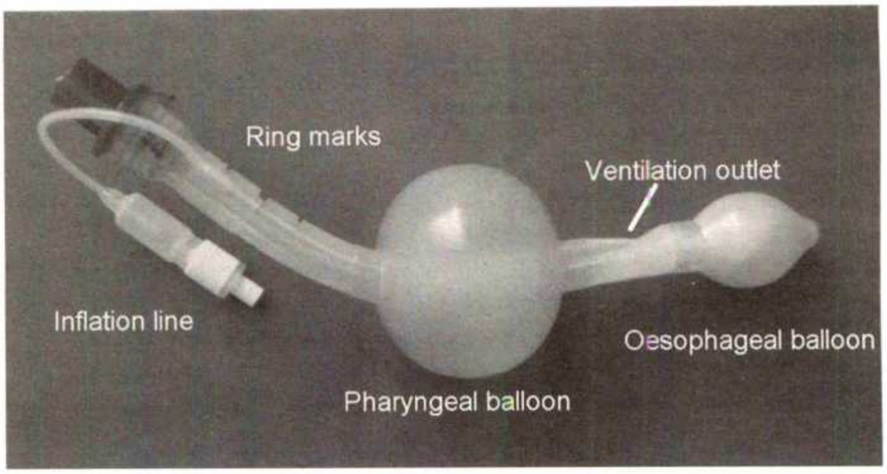


Fig 1 The laryngeal tube: a single lumen with an oesophageal and pharyngeal cuff that can both be inflated at the same time.

patency while other major airway interventions are anticipated or in progress'.[15]

Methods

Approval by the local research ethics committee was obtained. Adult patients scheduled for elective orthopaedic surgery and requiring tracheal intubation were asked to participate in this prospective study. All patients were ASA grade I or II; patients with severe pulmonary disease were not included. Patients were older than 18 yr; pregnancy and inability to give consent led to exclusion from the study. None of the patients had a history of airway difficulties during previous anaesthetics or showed signs of anatomical abnormalities; all were Mallampati 1 or 2.[16] Ten consecutive patients were recruited and gave written, informed consent. One anaesthetist with 4 yr of experience and special training in fibreoptic intubation performed all the manoeuvres after practising each step on a manikin during five training sessions.

Routine monitoring with electrocardiography, an automatic blood pressure cuff and a pulse oximeter was established before induction of general anaesthesia. Heart rate, blood pressure and oxygen saturation were recorded at all times. A drop in oxygen saturation below 95% at any point led to termination of the procedure, as did more than two attempts at the technique to be tested. Mask ventilation and tracheal intubation using a laryngoscope were then performed.

General anaesthesia was induced with fentanyl 1.0–1.5 μg kg^{-1} and 1% propofol 2–3 mg kg^{-1} after preoxygenation with oxygen 4 litres via face mask for 1 min. Initially, the patient's lungs were ventilated with a face mask-bag device. A size 4 or size 5 laryngeal tube was chosen according to the manufacturer's recommendations, and inserted blindly into the oropharynx without the use of neuromuscular blocking drugs, as demonstrated previously.[8 17 18] Both cuffs of the laryngeal tube were deflated completely, and the patient's head was placed in the neutral position. The tip of the laryngeal tube was introduced along the hard palate with one hand and was guided by the index finger of the opposite hand down the centre of the mouth. Insertion was continued until distinct resistance was felt and the printed ring marks on the tube were aligned with the front teeth. The cuffs were then inflated with 100 ml air using a syringe, and the tube was attached to the breathing system. Cuff pressure was recorded using a cuff pressure gauge. The manufacturer recommends a cuff pressure of 60–80 cm H_2O. Time for tube insertion was measured from removal of the face mask to finally positioning the laryngeal tube, and time for securing the airway was measured from inflation of the two cuffs to connecting the breathing system to the laryngeal tube. Adequate airway control was confirmed by auscultation over both lungs and the stomach. Additional verification of the correct position was confirmed by capnometry and bilateral chest expansion. When adequate ventilation had been achieved through the laryngeal tube, rocuronium 0.6 mg kg^{-1} was given for muscle relaxation.

After ventilation through the laryngeal tube for 1 min, the breathing system was disconnected and a flexible fibreoptic bronchoscope [model FI 10BS (Pentax, Hamburg, Germany), outer diameter 3.4 mm] with a mounted tube exchanger [Aintree Intubation Catheter (Cook Deutschland, Moenchengladbach, Germany), length 560 mm, inner diameter 4.8 mm, with a 15 mm Rapi-Fit™ Adapter (Cook Deutschland, Moenchengladbach, Germany), for use with tracheal tubes whose inner diameter is 7 mm or larger] was inserted through the laryngeal tube. The fibreoptic device was pushed forward until the larynx could be visualized. The exact position of the laryngeal tube in relation to the glottic structures was registered. Therefore the fibreoptic scoring system introduced by Brimacombe and Berry for the laryngeal mask airway[19] was used.

The glottis was then entered and the bronchoscope with the tube exchange catheter was advanced into the trachea

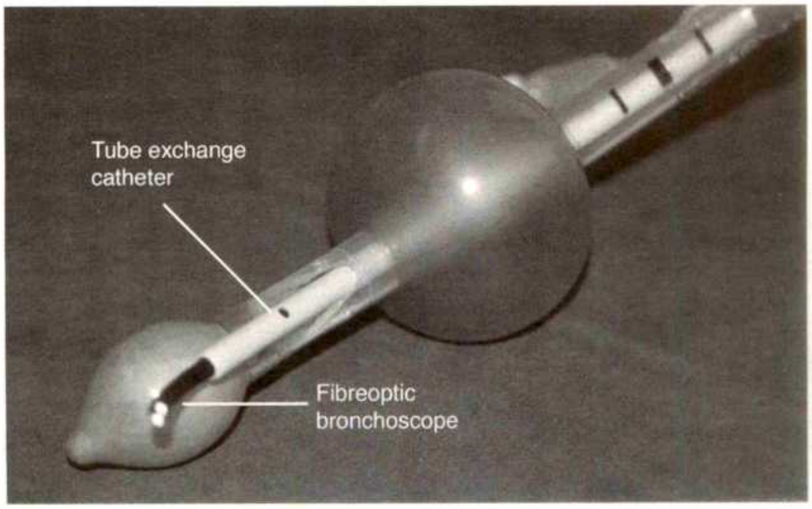


Fig 2 Flexible fibreoptic bronchoscope with mounted tube exchange catheter inserted in the laryngeal tube.

(Fig. 2). The flexible fibreoptic bronchoscope was removed. Both cuffs of the laryngeal tube were deflated completely and the device was removed carefully. The tube exchanger was left in place to railroad a tracheal tube [Lo-Contour™ (Murphy, Mallinckrodt Critical Care Inc., St Louis, MO, USA), inner diameter 7.5 mm] over it. When the tracheal tube was considered to be positioned in the trachea, the tube exchange catheter was removed.

After correct positioning of the tracheal tube had been verified fibreoptically and clinically, the breathing system was attached. Adequate ventilation was assessed by auscultation over the lungs and the stomach and by end-tidal capnometry. Time was measured from disconnecting the laryngeal tube from the breathing system to first ventilation through the tracheal tube.

Any difficulties during the procedure or after the operation, such as hoarseness, sore throat, dysphagia, bleeding and trauma, were recorded. Patients were assessed in the recovery area directly after transfer from the operating theatre, 6 h after the end of anaesthesia, and on the following day.

Results

Three female and seven male patients were included in the study. The mean (range) age of the 10 patients was 63.6 (46–81) yr, the mean (SD) weight was 72.1 (11.2) kg, and the mean (SD) height was 171.9 (7.0) cm.

The laryngeal tube was positioned without any difficulty at the first attempt and adequate ventilation and oxygenation was achieved in all patients. The mean (SD) time for positioning the laryngeal tube was 18.8 (3.4) s. Insertion time for the laryngeal tube was 10.4 (4.3) s, and 8.4 (2.5) s was needed to inflate the cuffs and secure the airway. A size 4 laryngeal tube was used twice, and a size 5 device eight times. All laryngeal tube cuffs were inflated with 100 ml air, resulting in a median cuff pressure of 80.5 cm H_2O (range 68–105 cm H_2O).

The fibreoptic view through the laryngeal tube was optimal in four cases, described as a grade 4 position in the classification by Brimacombe and Berry.[19] In two cases, an aryepiglottic fold and only parts of the vocal cords were seen initially. In another two cases only the aryepiglottic folds were visualized. Careful rotation of the laryngeal tube by approximately 40–60° (three times to the right and once to the left) improved the view in all four cases, resulting in a grade 4 position. In one case, the cords and the posterior epiglottis were seen (a grade 3 position). A jaw thrust manoeuvre allowed an optimal view of the glottic aperture, again resulting in a grade 4 position. In one patient, visualization of the glottis was not possible despite repeated manipulations of the tube (grade 1 position), resulting in failure of the tube exchange manoeuvre. Dislodgement of the laryngeal tube did not occur during any of the manipulations described.

Placement of the tracheal tube was achieved easily in eight patients. In three of these patients, slight rotation of the laryngeal tube was necessary to allow passage of the flexible fibreoptic bronchoscope into the trachea. Displacement of the tube exchange catheter occurred in one case, leading to oesophageal intubation, which was detected immediately. The tube exchange manoeuvre was performed successfully at the second attempt. When insertion of the tracheal tube over the tube exchange catheter was difficult, rotating the tube as recommended for standard fibreoptic intubation facilitated advancement into the trachea; no extensive manipulation of the jaw, as described for other devices,[15] was necessary in those patients in whom the manoeuvre was carried out successfully. The mean (SD) time for positioning the tracheal tube over the tube exchange catheter was 134.0 (36.2) s. The time for each intubation manoeuvre is given in Table 1; no improvement was detected with increasing experience.

No decline in oxygen saturation below 97% was recorded in any of the patients. No cardiovascular irregularities, such as tachycardia (heart rate greater 120 beats min^{-1}), bradycardia (heart rate under 50 beats min^{-1}), arrhythmias, hypotension or hypertension (blood pressure below 100/60 mm Hg or above 180/100 mm Hg), occurred during induction of anaesthesia or the exchange manoeuvres. The mean heart rate, mean oxygen saturation and the mean systolic and diastolic blood pressure during the procedures are given in Figure 3.

During postoperative examination of the patients, no injuries to the patients' teeth or lips or the mucosa of the mouth and oropharynx could be found. Two patients presented with minor complaints, one of slight hoarseness and a sore throat and one of mild hoarseness; both recovered fully by the day after surgery. In two patients, minimal mucosal lesions at the carina were observed during fibreoptic confirmation of the tracheal tube position. No correlation between difficulty positioning the tracheal tube and postoperative complaints could be detected.

Table 1 Individual tracheal intubation time, including exchange manoeuvre, for each patient

Patient	Time for tube exchange manoeuvre (s)
1	132.1
2	220.6
3	133.0
5	117.2
6	140.2
7	130.3
8	97.2
9	98.1
10	137.7
Mean	134.0

Discussion

Adverse respiratory events are a common complication in anaesthetized patients, often resulting in brain damage and death.[20] Approximately 600 people die each year worldwide from difficulties with intubation.[21] The incidence of difficult intubation for elective surgery ranges from 0.05 to 18%.[1] These and other results led to the 1993 ASA recommendations for the use of alternative airway adjuncts that allow adequate ventilation and oxygenation of patients.[2]

The laryngeal tube is a suitable airway management device with a high rate of successful insertion.[9 22] In our study, it was placed successfully at the first attempt in all patients without any ventilatory problems. As placement is considered easy,[22] its acceptance among physicians, nurses and paramedics is high.[9 23] Ventilation with the laryngeal tube is comparable to that with other devices.[8] Providing a good airway seal, the laryngeal tube has been shown to be efficacious during mechanical ventilation in adult and paediatric patients undergoing elective surgery.[7 24–26]

We have demonstrated for the first time the use of the laryngeal tube as an adjunct to ventilation and oxygenation and a guide to viewing the larynx and subsequently positioning a tracheal tube. The experience is encouraging, especially because oxygen administration is possible at every stage of the manoeuvre. Difficulty positioning the Aintree catheter occurred in only one patient in our study; in this patient the glottic aperture could not be visualized, yet adequate ventilation was possible at all times through the laryngeal tube. Initial oesophageal intubation in one patient was probably caused by displacement of the tube exchange catheter during railroading of the tracheal tube. Correct tracheal positioning of the Aintree catheter had been confirmed during fibreoptic-guided placement, but removal of the laryngeal tube when the catheter tip lay close to the glottis may have led to dislodgement. This can also occur

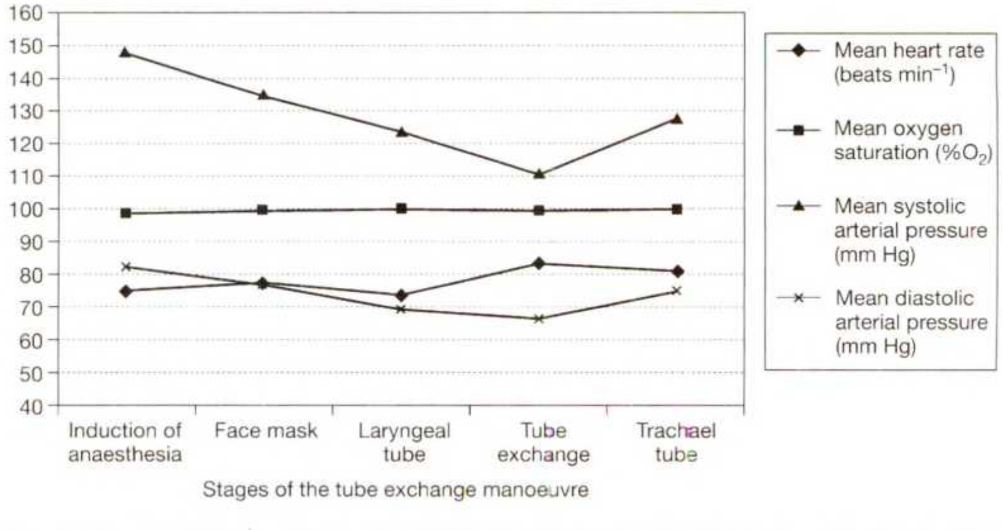


Fig 3 Changes in mean heart rate (beats min^{-1}), mean oxygen saturation (%) and mean systolic and diastolic arterial blood pressure (mm Hg) at each stage of the tube exchange manoeuvre.

when railroading a tracheal tube over a fibreoptic bronchoscope that is not inserted far enough into the trachea.

A comparable procedure has been described for the laryngeal mask airway[13] and the cuffed oropharyngeal airway (COPA).[14] In general, the concept of the 'dedicated airway' will not only help to master difficult intubation but also allow training in fibreoptic intubation, even in patients known to be difficult to intubate under safe conditions.[15] The time needed for inserting the tracheal tube was comparable to that achieved with the COPA.[14] Because of a different protocol, comparison with the insertion times described for the laryngeal mask airway is not possible. In contrast to the latter study, no improvement with practice was observed in our study, probably as a result of prior manikin practice.

An important advantage of the laryngeal tube is its stable positioning even when manipulation is necessary to improve the view of the glottic aperture. Additionally, the specific configuration of the aperture of the laryngeal tube guides the tip of the flexible fibreoptic bronchoscope more towards the glottis than would be the case with the standard laryngeal mask airway.

As the glottic aperture could not be visualized in all patients without manipulation of the laryngeal tube, blind insertion of an exchange bougie without fibreoptic control, as described for other airway devices,[27 28] cannot be recommended. The fact that the position of the laryngeal mask airway during fibreoptic control was only central in 59% of cases[29] supports the idea of using a fibreoptic bronchoscope rather than inserting a tube exchange catheter blindly through any airway device. Because of the variable position of the blindly inserted laryngeal mask airway with respect to the glottic aperture,[30] use of a fibreoptic bronchoscope also increases the success rate of tracheal intubation via a laryngeal mask.[31]

The manoeuvre described in this study allows a high degree of control of the patient's airway. Continuous application of oxygen into the trachea is possible via the laryngeal tube and the tube exchange catheter. The oxygen saturation did not fall below 97% and jet ventilation via the Aintree catheter, which is an option when managing difficult airways for a limited period, was not required. Haemodynamic side-effects, as reported with the intubating laryngeal mask airway,[32] did not occur during the tube exchange manoeuvre via the laryngeal tube.

The concept of oxygenation being more important than the intubation is an essential part of recommendations for managing the difficult airway.[2] Because the laryngeal tube might be an important alternative for managing the difficult airway, a technique for subsequently placing a tracheal tube over this device should be considered after initial oxygenation problems have been solved. Thorough planning for airway emergencies should always include procedures that allow administration of oxygen at any time, as this is an important factor in improving patient outcome after critical incidents. Fibreoptic control of the tube position guarantees a maximum degree of patient safety.

Postoperative airway examination showed no severe trauma induced by insertion of the laryngeal tube or the tube exchange catheter. Visible lesions of the upper airway, such as haematoma and mucosal laceration, as described most often for the Combitube,[33] did not occur in any of the patients studied. Mild hoarseness and a slight sore throat are common postoperative complaints after tracheal intubation or the use of a laryngeal mask airway or the Combitube.[34] The incidence of postoperative airway discomfort depends on the airway management device. A sore throat and dysphagia are most common after placement of the Combitube, with an incidence of 48 and 68% respectively.[33] After use of the laryngeal mask airway, patients suffer from dysphagia in 33% of cases.[35] This complaint is significantly less frequent in patients undergoing tracheal intubation.[36] In our study, no case of dysphagia was recorded, although two airway devices were placed. Tracheal intubation is considered the main cause of hoarseness.[33] The incidence ranges from 14.4%[37] to 32%.[38] Although in our study the tracheal tube was inserted over the tube exchange catheter without direct visualization of its passage through the vocal cords, only two of the 10 patients complained of hoarseness. Mucosal lesions on the carina in two of the patients were probably induced by the rigid tip of the tube exchange catheter, which was held in place during removal of the laryngeal tube. This problem might be solved by a catheter with a softer distal tip.

There are limitations of this study. As none of the patients presented with a difficult airway, the feasibility of this technique should also be evaluated under these conditions. Comparison of the performance of physicians at various stages of their training might help in judging the usefulness of the manoeuvre described here.

Acknowledgements

The laryngeal tubes used in this study were provided by VBM Medizintechnik, Sulz a.N., Germany. Tube exchange catheters were provided by Cook Deutschland, Moenchengladbach, Germany. The flexible fibreoptic bronchoscope was provided by Pentax, Hamburg, Germany. No financial support was received for the study or preparation of the manuscript.

References

1 Benumof JL. Management of the difficult adult airway. *Anesthesiology* 1991; **75**: 1087–110

2 American Society of Anesthesiologists. Practice guidelines for management of the difficult airway. A report by the American Society of Anesthesiologists Task Force on management of the difficult airway. *Anesthesiology* 1993; **78**: 597–602

3 Genzwuerker H, Hilker T, Hohner E, Kuhnert-Frey B. Der Larynxtubus: Eine Alternative für die vorübergehende Oxygenierung bei schwieriger Intubation? [abstract]. *Anaesthesiol Intensivmed* 1999; **40**: 402

4 Genzwuerker HV, Dhonau S, Ellinger K. Use of the laryngeal

tube for out-of-hospital resuscitation. *Resuscitation* 2002; **52**: 221–4

5 Finteis T, Genzwuerker H, Becker F, Ellinger K. Use of the laryngeal tube in a polytraumatized patient [German]. *Notfall Rettungsmed* 2001; **4**: 511–14

6 Genzwuerker HV, Kuhnert-Frey B. Modification of the Laryngeal Tube. *Prehosp Emerg Care* 2000; **4**: 371–2

7 Asai T, Murao K, Shingu K. Efficacy of the laryngeal tube during intermittent positive-pressure ventilation. *Anaesthesia* 2000; **55**: 1099–102

8 Doerges V, Ocker H, Wenzel V, Schmucker P. The laryngeal tube: a new simple airway device. *Anesth Analg* 2000; **90**: 1220–2

9 Genzwuerker HV, Hilker T, Hohner E, Kuhnert-Frey B. The laryngeal tube: a new adjunct for airway management. *Prehosp Emerg Care* 2000; **4**: 168–72

10 Ocker H, Doerges V, Heringslake M, Schmucker P. Der neue Larynxtubus vs. Larynxmaske—suffiziente Beatmung mit Aspirationsschutz? [abstract]. *Anaesthesiol Intensivmed* 2000; **41**: 376

11 Robertson C, Steen P, Adgey J, *et al.* The 1998 European Resuscitation Council guidelines for adult advanced life support: a statement from the Working Group on Advanced Life Support, and approved by the executive committee. *Resuscitation* 1998; **37**: 81–90

12 Coppolo DP, May JJ. Self-extubations. A 12-month experience. *Chest* 1990; **98**: 165–9.

13 Atherton DPL, O'Sullivan E, Lowe D, Charters P. A ventilation-exchange bougie for fibreoptic intubations with the laryngeal mask airway. *Anaesthesia* 1996; **51**: 1123–6

14 Hawkins M, O'Sullivan E, Charters P. Fibreoptic intubation using the cuffed oropharyngeal airway and Aintree intubation catheter. *Anaesthesia* 1998; **53**: 891–4

15 Charters P, O'Sullivan E. The 'dedicated airway': a review of the concept and an update of current practice. *Anaesthesia* 1999; **54**: 778–86

16 Mallampati SR, Gatt SP, Gugino LD, *et al.* A clinical sign to predict difficult tracheal intubation: a prospective study. *Can Anaesth Soc J* 1985; **32**: 429–34

17 Gaitini LA, Somri M, Vaida SJ, Yanovski B, Capdevila M. The laryngeal tube in paediatric anaesthesia. *Eur J Anaesthesiol* 2001; **18**: 105

18 Genzwürker HV, Finteis T, Kuhnert-Frey B, Ellinger K. Use of the laryngeal tube for short interventions in gynaecology. *Eur J Anaesthesiol* 2001; **18**: 53–4

19 Brimacombe J, Berry A. A proposed fiber-optic scoring system to standardize the assessment of laryngeal mask airway position. *Anesth Analg* 1993; **76**: 457

20 Caplan RA, Posner KL, Ward RJ, Cheney FW. Adverse respiratory events in anesthesia: a closed claims analysis. *Anesthesiology* 1990; **72**: 828–33

21 King TA, Adams AP. Failed tracheal intubation. *Br J Anaesth* 1990; **65**: 400–14

22 Galli B, Mattei A, Antonelli S, Barzoi G, Agrò F. A new adjunct for airway management: the laryngeal tube, preliminary data. *Eur J Anaesthesiol* 2001; **18**: 124

23 Finteis T, Genzwuerker H, Blankenburg A, Ellinger K, Kuhnert-Frey B. Airway management by nonmedical personnel: a prospective, randomized comparison of laryngeal masks, combitubes, and laryngeal tubes [German]. *Notfall Rettungsmed* 2001; **4**: 327–34

24 Agrò F, Cataldo R, Alfano A, Galli B. A new prototype for airway management in an emergency: the laryngeal tube. *Resuscitation* 1999; **41**: 284–6

25 Lecomte J, Brehm-Arnold S, Goubaux B, Langeron O, Cros AM. Clinical evaluation of the laryngeal tube or LT in adult patients. *Anesthesiology* 2000; **93**: A564

26 Richebe P, Semjen F, El Hammar F, Marie S, Cros AM. Clinical evaluation of the laryngeal tube (LT) in pediatric anesthesia. *Anesthesiology* 2000; **93**: A1268

27 Allison A, McCrory J. Tracheal placement of a gum elastic bougie using the laryngeal mask airways. *Anaesthesia* 1990; **45**: 419–20

28 Dimitriou V, Voyagis GS. Light-guided tracheal intubation using a prototype illuminated flexible catheter through the intubating laryngeal mask. *Eur J Anaesthesiol* 1999; **16**: 448–53

29 Fuellekrug B, Pothmann W, Werner C, Schulte am Esch J. The laryngeal mask airway: gas leakage and fiberoptic control of positioning. *J Clin Anesth* 1993; **5**: 357–63

30 Payne J. The use of fibreoptic laryngoscope to confirm the position of the laryngeal mask. *Anaesthesia* 1989; **44**: 865

31 Silk JM, Hill HM, Calder I. Difficult intubation and the Laryngeal Mask. *Eur J Anaesthesiol* 1991; **8** (Suppl 4): 47–51

32 Kihara S, Yaguchi Y, Watanabe S, Brimacombe J, Taguchi N, Yamasaki Y. Haemodynamic responses to the intubating laryngeal mask and timing of removal. *Eur J Anaesthesiol* 2000; **17**: 744–50

33 Oczenski W, Krenn H, Dahaba AA, *et al.* Complications following the use of the Combitube, tracheal intubation and laryngeal mask airway. *Anaesthesia* 1999; **54**: 1161–5

34 McHardy FE, Chung F. Postoperative sore throat: cause, prevention and treatment. *Anaesthesia* 1999; **54**: 444–53

35 Rieger A, Brunne B, Striebel HW. Intracuff pressures do not predict laryngopharyngeal discomfort after use of the laryngeal mask airway. *Anesthesiology* 1997; **87**: 63–7

36 Rieger A, Brunne B, Hass I, *et al.* Laryngo-pharyngeal complaints following laryngeal mask airway and endotracheal intubation. *J Clin Anesth* 1997; **9**: 42–7

37 Christensen AM, Willemoes-Larsen H, Lundby L, Jakobsen KB. Postoperative throat complaints after tracheal intubation. *Br J Anaesth* 1994; **73**: 786–7

38 Jones MW, Catling S, Evans E, Green DH, Green JR. Hoarseness after tracheal intubation. *Anaesthesia* 1992; **47**: 213–16

British Journal of Anaesthesia **89** (**5**): 739–46 (2002)

BJA

LABORATORY INVESTIGATION

Neuroprotective and neurotoxic properties of the 'inert' gas, xenon

D. Ma[1], S. Wilhelm[1], M. Maze[1 2] * † and N. P. Franks[1 2 †]

[1]Magill Department of Anaesthesia, Chelsea and Westminster Hospital and [2]Biophysics Group, The Blackett Laboratory, Imperial College of Science, Technology and Medicine, London, UK

**Corresponding author: Department of Anaesthetics and Intensive Care, Faculty of Medicine, Imperial College, Chelsea and Westminster Hospital, 369 Fulham Road, London SW10 9NH, UK*

Background. Antagonists of the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptors have been shown not only to have neuroprotective effects but also to exhibit neurotoxic properties. In this study, we used c-Fos, a protein product of an immediate early gene, as a marker of neuronal injury to compare the neuroprotective effects of xenon and the neurotoxic properties of xenon, nitrous oxide, and ketamine, three anaesthetics with NMDA receptor antagonist properties.

Methods. We used an *in vivo* rat model of brain injury in which *N*-methyl-DL-aspartic acid (NMA) is injected subcutaneously (s.c.) and c-Fos expression in the arcuate nucleus is used as a measure of injury. To examine the neurotoxic potential of each of the three anaesthetics with NMDA receptor antagonist properties, c-Fos expression in the posterior cingulate and retrosplenial (PC/RS) cortices was measured.

Results. Xenon dose-dependently suppressed NMA-induced c-Fos expression in the arcuate nucleus with an IC_{50} of 47 (2)% atm. At the highest concentration tested (75% atm) NMA-induced neuronal injury was decreased by as much as that observed with the prototypical NMDA antagonist MK801 (0.5 mg kg^{-1} s.c.). Both nitrous oxide and ketamine dose-dependently increased c-Fos expression in PC/RS cortices; in contrast, xenon produced no significant effect. If the dopamine receptor antagonist haloperidol was given before either nitrous oxide or ketamine, their neurotoxic effects were eliminated.

Conclusions. Uniquely amongst anaesthetics with known NMDA receptor antagonist action, xenon exhibits neuroprotective properties without co-existing neurotoxicity. The reason why ketamine and nitrous oxide, but not xenon, produce neurotoxicity may involve their actions on dopaminergic pathways.

Br J Anaesth 2002; **89**: 739–46

Keywords: anaesthetics gases, nitrous oxide; anaesthetics gases, xenon; anaesthetics i.v., ketamine; brain, arcuade nucleus; brain, posterior cingulate and retrosplenial cortices; protein, c-Fos

Accepted for publication: July 1, 2002

Although glutamate is probably the most important excitatory neurotransmitter in the mammalian brain and is essential for normal brain function, the presence of excessive amounts of glutamate can lead to cell death. The term excitotoxicity, first coined by Olney,[1] denotes the process whereby activation of glutamate receptors, especially those of the *N*-methyl-D-aspartate (NMDA) subtype, leads to excess calcium entry into cells which in turn triggers a

---

[†] *Declaration of interest.* Professor Maze and Professor Franks are Board members of an Imperial College spin-out company (Protexeon Ltd) that is interested in developing clinical applications for medical gases, including xenon. Both Professor Franks and Professor Maze are paid consultants in this activity. In addition, Air Products have funded, and continue to fund, work in the authors' laboratories that bears on the actions of xenon as an anaesthetic and neuroprotectant and Air Products has a financial stake in Protexeon Ltd. However, none of the work described in this manuscript was funded by either company.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

biochemical cascade resulting in neuronal death. Neurotoxicity induced by over-activation of NMDA receptors is thought to sustain ongoing neuronal injury and death in acute processes such as stroke and head trauma, as well as in chronic neurodegenerative disorders.[2] Consistent with this, a large body of evidence has shown that NMDA receptor antagonists can be neuroprotective in both *in vitro* and *in vivo* models of neuronal injury[3–6] and can prevent deterioration of cognitive function after cardiopulmonary bypass.[7]

Xenon, a noble gas with anaesthetic properties, has recently been found to be an NMDA receptor antagonist;[8 9] another gaseous anaesthetic, nitrous oxide can also inhibit the NMDA receptor.[10] Consequently, these two gases might be considered good candidates as neuroprotectants because they can be easily administered and rapidly enter the brain. However, a major deterrent to the use of NMDA antagonists as neuroprotective agents is the profound psychotomimetic behavioural changes which such drugs can produce.[11] Histological data in studies conducted with the NMDA receptor antagonists ketamine, phencyclidine (PCP), and dizolcipine maleate (MK801) revealed pyramidal neuronal damage in the region of the posterior cingulate and retrosplenial (PC/RS) cortices,[12 13] which may underlie these behavioural changes; similar pathological changes have been reported with nitrous oxide.[14] Whether or not NMDA antagonism alone is sufficient to produce this neurotoxicity, however, is not known and it is possible that perturbation of other neurotransmitter systems is involved. For example, NMDA receptor antagonists including ketamine and nitrous oxide, can activate dopamine receptors or increase dopamine release both *in vivo* and *in vitro*.[15–17] Moreover, major antipsychotics with dopamine D2 receptor antagonist properties can prevent ketamine's psychotomimetic side-effects.[18] In addition, a recent *in vitro* study suggests that xenon can decrease dopamine release.[19]

The aims of the present study were to determine: (i) whether xenon has a neuroprotective effect in an *in vivo* model of neuronal excitotoxicity; (ii) whether xenon exhibits typical NMDA receptor antagonist neurotoxicity in the PC/RS cortices; and (iii) whether dopamine contributes to the neurotoxicity exhibited by anaesthetics with NMDA receptor antagonist properties. We used an immediate early gene (c-*fos*)-encoded protein (c-Fos), in order to assess neuronal injury as reported previously.[20–24]

Methods

This study conforms to the United Kingdom Animals (Scientific Procedures) Act of 1986.

Effect of xenon on NMA-induced c-Fos expression in the arcuate nucleus

Nine groups (n=3–4 in each group) of female Sprague–Dawley rats (240–260 g) were treated randomly as follows: group 1 received NMA, 100 mg kg^{-1} body wt subcutaneously (s.c.), and was exposed to 25% oxygen and 75% nitrogen; groups 2–5 were exposed to either 20, 40, 60, or 75% xenon plus 25% oxygen (with the remainder being nitrogen, where necessary) for 15 min before injection of NMA, 100 mg kg^{-1} s.c.; group 6 was exposed to 25% oxygen and 75% nitrogen, and received saline, 8 ml kg^{-1} s.c.; group 7 received 75% xenon and 25% oxygen for 15 min before injection of saline 8 ml kg^{-1} s.c.; group 8 was exposed to 25% oxygen and 75% nitrogen; and received MK801, 0.5 mg kg^{-1} s.c.; group 9 was exposed to 25% oxygen and 75% nitrogen; and received MK801 0.5 mg kg^{-1} s.c., followed by NMA, 100 mg kg^{-1} s.c. 15 min later. Doses of NMA and MK801 were selected from a previous study.[14] Female animals were used because this gender has been shown to be more sensitive to excitotoxins, particularly for NMDA antagonists that are rapidly metabolized;[25] for agents that are less susceptible to metabolism, such as nitrous oxide, neurotoxicity is the same for both sexes.[25] Rats were randomly assigned between groups without reference to the day in their oestrous cycle.

Neurotoxicity of xenon, nitrous oxide, ketamine, and MK801

Eleven groups (n=3 in each group) of animals were treated as follows: group 1 was exposed to 25% oxygen and 75% nitrogen; groups 2–4 were exposed to 40, 60, or 75% xenon, plus 25% oxygen (with the remainder being nitrogen, where necessary) for 90 min; groups 5–7 were exposed to 40, 50, or 60% nitrous oxide, plus 25% oxygen (with the remainder being nitrogen) for 90 min; groups 8–10 received ketamine, 25, 50, or 100 mg kg^{-1} s.c., respectively, and were exposed to 25% oxygen and 75% nitrogen; group 11 received MK801, 0.5 mg kg^{-1} s.c. and was exposed to 25% oxygen and 75% nitrogen. Doses of ketamine were selected on the basis of a previous study,[12] and were below those necessary to induce a loss of righting reflex.

Effect of dopamine D2 receptor antagonist haloperidol on nitrous oxide- and ketamine-induced neurotoxicity

Five groups (n=3 in each group) of animals were treated randomly as follows: group 1 received saline, 2 ml kg^{-1} s.c. and were exposed to 75% nitrogen and 25% oxygen; group 2 received saline before exposure to 75% nitrous oxide and 25% oxygen for 90 min; group 3 received haloperidol 2.5 mg kg^{-1} s.c., 30 min before exposure to 75% nitrous oxide and 25% oxygen for 90 min; group 4 received saline, 2 ml kg^{-1} s.c., before ketamine 50 mg kg^{-1} s.c.; group 5 received haloperidol 2.5 mg kg^{-1} s.c., 30 min before ketamine 50 mg kg^{-1} s.c.

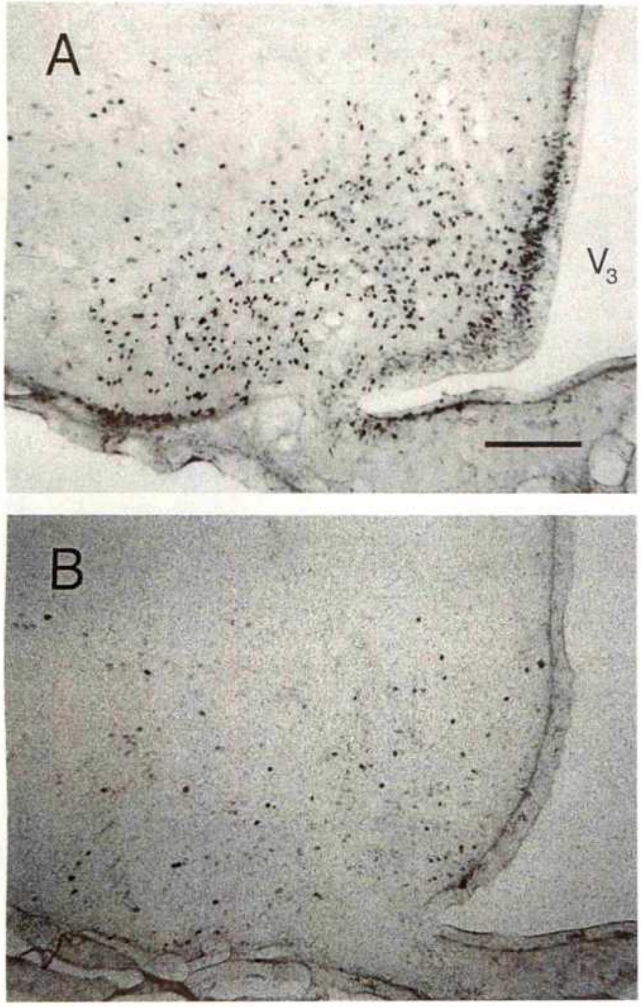


Fig 1 Representative coronal sections showing half of the arcuate nucleus of the hypothalamus stained for c-Fos positive immunoreactivity. (A) Three hours after subcutaneous injection of NMA (100 mg kg^{-1}) the c-Fos positive neurons are easily visualised by dense black staining. (B) For animals injected with NMA but also exposed to 75% xenon there was a marked reduction in the number of c-Fos positive neurons. The scale bar represents 100 μm and the third ventricle is marked V_3.

Gas exposure

During exposure to 20, 40, 60, and 75% xenon or 40, 60, and 75% nitrous oxide as mentioned above, the gas mixture was introduced into a chamber (International Market Supply, Cheshire, UK) using calibrated flow meters. After a flush at a flow rate of 4 litres min^{-1} for 3 min, the flow rate was reduced to 40 ml min^{-1} for maintenance. The humidity in the chamber was maintained between 40 and 60% using silica gel (Merck, Leicestershire, UK) and the carbon dioxide level was maintained below 0.6% with soda lime.

Perfusion, brain harvesting, and tissue processing

For excitotoxicity experiments, rats were killed 3 h after NMA administration. For neurotoxicity experiments, rats were killed 90 min after exposure. Animals were deeply anaesthetized with sodium pentobarbital 100 mg kg^{-1} i.p. perfused transcardially with 100 ml heparinized saline followed by 4% paraformaldehyde 500 ml in 0.1 M phosphate buffer. The whole brain was removed and further fixed in 4% paraformaldehyde in 0.1 M phosphate-buffered saline (PBS) overnight. The appropriate area of brain was sliced and embedded in paraffin. For c-Fos staining in the arcuate nucleus (excitotoxicity experiments), three sections (25 μm) were cut midway between the rostral and caudal boundaries of the arcuate nucleus. For c-Fos staining of the PC/RS cortices (neurotoxicity experiments), three sections (25 μm) were cut 6 mm caudal to the bregma at which site the maximal lesion had been noted in a previous study.[14] Sections were dewaxed with 100% xylene, dehydrated with various concentrations of ethanol and finally floated in PBS for immunohistochemistry.

Immunohistochemistry

Sections were incubated for 30 min in 0.3% H_2O_2 in methanol in order to quench endogenous peroxidase and thereafter washed three times in PBS. Following this, the sections were incubated for 1 h in a 'blocking solution' consisting of 3% donkey serum and 0.3% Triton X in PBS (PBT) and subsequently incubated overnight at 4°C in 1:6000 goat anti-c-Fos antibody (sc-52-G, Santa Cruz Biotechnology, Santa Cruz, CA) in PBT with 1% donkey serum. The sections were then rinsed three times with PBT and incubated with 1:200 donkey anti-goat IgG (Vector Laboratories, Burlingame, CA) in PBT with 1% donkey serum for 1 h. The sections were washed again with PBT and incubated with avidin–biotin–peroxidase complex (Vector Laboratories) in PBT for 1 h. The sections were rinsed three times with PBS and stained with 3,3′-diaminobenzidine (DAB) with nickel ammonium sulphate to which hydrogen peroxide was added (DAB kit, Vector Laboratories) to achieve immunohistochemical visualization. When the staining was complete, the sections were rinsed in PBS followed by distilled water and mounted on glass slides, dehydrated with 100% ethanol, cleared with 100% xylene, and covered with cover slips. Unless otherwise mentioned, all reactions were performed at room temperature.

Quantitative counting of c-Fos neurons

The sections were photographed using a digital camera (model C2020Z, Olympus Optical, Southhall Middlesex, UK) attached to a microscope (Olympus model BX50). Under identical conditions, photographs were taken from each of the three sections per animal and counted for c-Fos positive neurons (dense black nuclear staining; see Fig. 1) by an author who was blinded to the treatment. The sum of c-Fos positive neurons for the three representative sections was the aggregate score of each animal for either the arcuate nucleus or PC/RS cortices and results are reported as mean

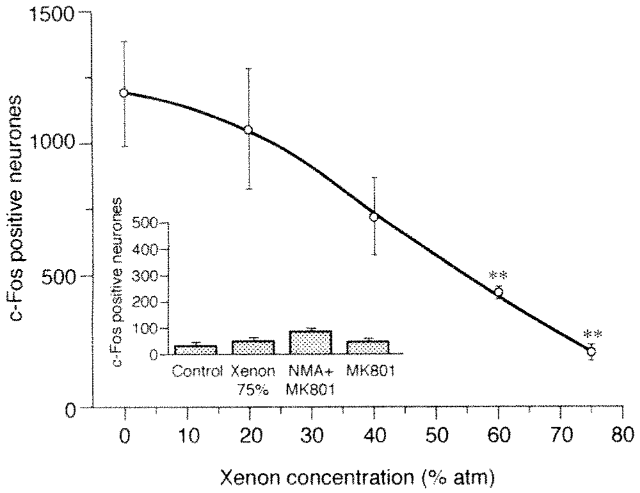


Fig 2 Mean number of NMA-induced c-Fos positive neurones in the arcuate nucleus of the hypothalamus is greatly reduced by xenon. Data are mean (SEM). $^{**}P<0.01$ relative to NMA treatment alone. The inset shows data from control animals injected with saline and the lack of effect when xenon is applied alone (i.e. in the absence of NMA). The inset also presents results from a positive control showing that MK801 (0.5 mg kg^{-1}) in the presence of NMA reduces the number of c-Fos positive neurones to control levels while having no effect *per se*.

(SEM). The statistical analysis was performed by one-way analysis of variance, followed by Newman–Keuls test. A P value <0.05 was regarded as statistically significant.

Results

NMA-induced excitotoxicity in the arcuate nucleus of the hypothalamus, the effects of xenon and MK801

Subcutaneously injected NMA (100 mg kg^{-1}) produced a large number of c-Fos positive neurones in the arcuate nucleus of the hypothalamus (1188 (197), mean (SEM)) that was greatly in excess of the number (37 (8)) observed in control animals injected with saline. Figure 1A is a representative section showing c-Fos positive neurones in the arcuate nucleus following NMA treatment. Xenon exposure produced a marked and concentration-dependent reduction in the number of c-Fos positive neurones (Figs 1B and 2) with an IC$_{50}$ of 47 (2)% atm. At the highest concentration tested (75% atm) the number of c-Fos positive neurones did not differ significantly from the number observed in saline-injected animals (P>0.05). In addition, the number of c-Fos positive neurones from animals exposed to xenon alone at the highest concentration investigated (75% atm) did not differ significantly (P>0.05) from animals exposed to nitrogen (Fig. 2, inset). As a positive control we tested the ability of the prototypical NMDA antagonist MK801 to block the induction of c-Fos positive neurones in the hypothalamus. MK801 0.5 mg kg^{-1} (Fig. 2, inset) injected s.c. reduced the number of NMA-induced c-Fos positive neurones to a value (89 (23)) that was comparable with that found in the presence of 75% xenon (Fig. 2).

Neurotoxicity in the posterior cingulate and retrosplenial cortices following administration of xenon, nitrous oxide, ketamine, and MK801

Using c-Fos expression in layers III/IV of the posterior cingulate and retrosplenial cortices as a marker for neurotoxicity, we investigated the extent to which the NMDA antagonists xenon, nitrous oxide, ketamine, and MK801 exhibited neurotoxicity alone. Figure 3 illustrates representative sections showing the posterior cingulate and retrosplenial cortices following various treatments. In control animals (Figs 3A and 4) the number of c-Fos positive neurones was only 109 (29) and this did not change significantly (P>0.05) in the presence of xenon up to 75% atm (Figs 3B and 4). This was in marked contrast to the effects of nitrous oxide (Figs 3C and 4) and ketamine (Figs 3D and 4), both of which increased the number of c-Fos positive neurones in a dose-dependent manner. As a positive control, the effects of MK801 at the dose (0.5 mg kg^{-1}) that we had observed gave maximum neuroprotection to the neurotoxic effects of NMA were investigated (Fig. 2, inset). This dose of MK801 produced a large and highly significant increase in the number of c-Fos positive neurones in the posterior cingulate and retrosplenial cortices.

Effect of haloperidol on nitrous oxide- and ketamine-induced neurotoxicity

The extent to which the neurotoxicity produced by nitrous oxide and ketamine could be blocked by the dopamine D2 receptor antagonist haloperidol was investigated. Pretreatment with haloperidol greatly decreased the number of c-Fos positive neurones induced by either nitrous oxide or ketamine alone (Fig. 5), and for both agents haloperidol pretreatment reduced the induction of c-Fos positive neurones to a level comparable with that found in control animals (Fig. 5).

Discussion

c-Fos as a rapid and sensitive indicator of neuroneal injury

The *c-fos* gene, a member of a class of immediate early genes, is readily induced by a variety of physiological and pathological factors. For example, noxious stimulation including peripheral sensory stimulation, seizures, and that caused by pharmacological agents including glutamate receptor agonists and antagonists, can cause an increase of *c-fos*-encoded protein in the spinal cord or higher brain centres.[20–23] Thus, while c-Fos protein is a neuroneal

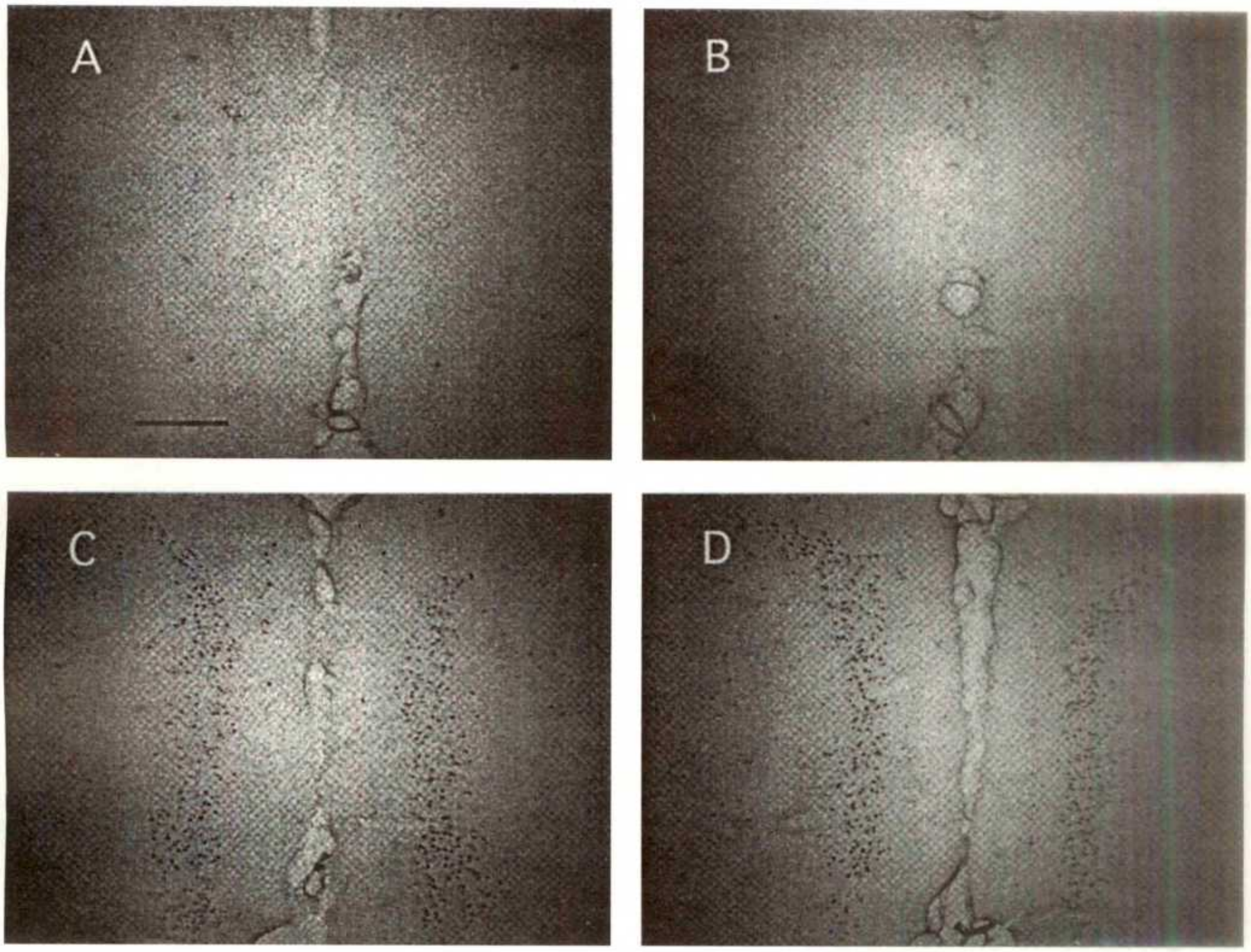


Fig 3 Nitrous oxide and ketamine but not xenon are neurotoxic. Representative coronal sections showing the posterior cingulate and retrosplenial cortices stained for c-Fos positive immunoreactivity. (A) Control. (B) Ninety minutes after exposure to 75% xenon. (C) Ninety minutes after exposure to 75% nitrous oxide. (D) Ninety minutes after s.c. injection of ketamine 100 mg kg^{-1}. The scale bar represents 100 μm.

marker for neuroneal stress induced by non-lethal stimulation, under certain conditions, including exposure to excessive amounts of NMDA receptor agonists or antagonists, c-Fos protein can be used as a marker for neuroneal injury before cell death or apoptosis.[23 26] Furthermore, *c-fos* gene induction and its protein expression precedes heat-shock protein expression (a known cell stress indicator which is not induced by normal physiological stimuli) or histopathological changes.[12 27] Therefore, the protein encoded by the *c-fos* gene can be used as a rapid and sensitive marker of neuroneal injury when neurones are under lethal stress and, although there may not be a direct causal link, c-Fos expression has been used as an indicator to measure both neuroprotection by, as well as neurotoxicity of, NMDA antagonists.[20 22]

Neuroprotection by xenon

One of the aims of the present study was to use c-Fos as a marker for neuroneal injury to examine whether or not xenon could act as a neuroprotectant. We used an *in vivo* paradigm that involves the induction of a selective type of neuroneal injury in the arcuate nucleus of the hypothalamus following s.c. injection of a glutamate receptor agonist, NMA. Excessive activation of the NMDA subtype of the glutamate receptor produces excitotoxicity, which is implicated in both acute (e.g. stroke, seizures, hypoxia, trauma) and chronic (e.g. Huntington's disease) neuroneal injury.[2] Moreover, some NMDA receptor antagonists have shown remarkable efficacy in experimental models of neuroneal injury[3–6] although this promise has not been translated into clinical utility. One of the possible reasons for the failure to translate this neuroprotective potential to clinical use may be the difficulty that most NMDA receptor antagonists have in penetrating the blood–brain barrier and reaching the effect site. Xenon, however, is a small apolar atom that rapidly reaches equilibrium with the brain when present in the inspired gas. Our results show that, at concentrations that are easily attainable at normal pressures, xenon is an effective neuroprotectant (Figs 1 and 2). Indeed, at the

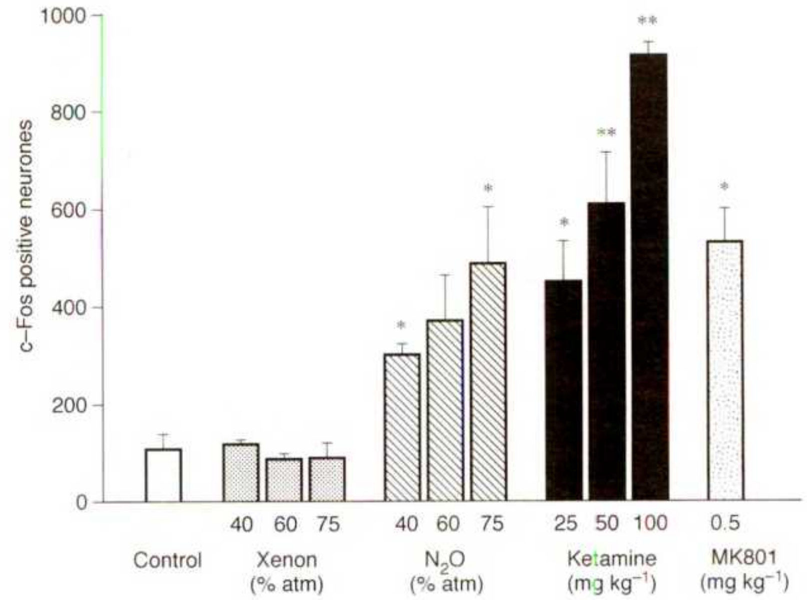


Fig 4 Concentration or dose–response effects of xenon, nitrous oxide, and ketamine on the number of c-Fos positive neurons in the posterior cingulate and retrosplenial cortices. Results are means (SEM). $*P<0.05$; $**P<0.01$ relative to control. The data for MK801 (0.5 mg kg^{-1}), a prototypical NMDA receptor antagonist are presented as a positive control.

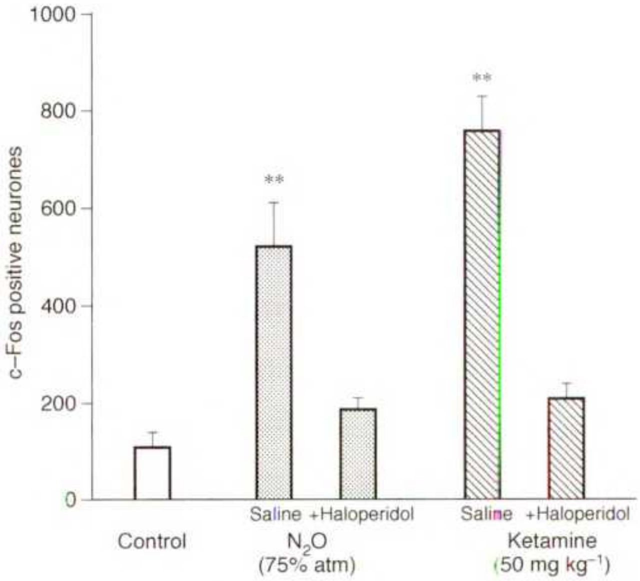


Fig 5 Haloperidol, a dopamine D2 receptor antagonist, blocks nitrous oxide and ketamine-induced neurotoxicity. Data show the number of c-Fos positive neurones in the posterior cingulate and retrosplenial cortices following exposure to 75% nitrous oxide or s.c. injection of ketamine (50 mg kg^{-1}) compared with control. Results are means (SEM). $**P<0.01$ relative to control.

highest concentration we tested (75% atm), which is close to the concentration required for surgery,[28 29] the neuroprotection achieved was comparable with that obtained using the potent NMDA receptor antagonist MK801 (Fig. 2, inset).

Neurotoxicity of NMDA antagonists

Although NMDA receptor antagonists have neuroprotective properties, they can also cause psychotomimetic effects in humans and abnormal locomotor activities in rodents.[12 30] A neuroneal correlate (although not necessarily the cause) of the ability to produce these behavioural effects is the damage which NMDA antagonists produce in PC/RS cortices[12] which can be assessed by c-Fos expression.[22 31] The data in Figures 3 and 4 show that, unlike nitrous oxide, ketamine and MK801, xenon had no effect on c-Fos expression in PC/RS cortices, and that concentrations of xenon that gave maximum neuroprotection (75% atm) showed no intrinsic neurotoxicity. This corroborates recent work on the neurotoxicity of nitrous oxide and ketamine[14 25] and a study[32] that showed nitrous oxide enhanced the neurotoxicity induced by ketamine while this was inhibited by xenon. The observation that xenon is able to counteract the neurotoxic effects of ketamine, for which there is strong evidence of NMDA receptor involvement,[10 12] suggests that xenon, in addition to its ability to inhibit NMDA receptors, is likely to have additional targets.

It has been suggested that the behavioural changes produced by ketamine, phencyclidine, and MK801 in healthy individuals are similar to those seen in schizophrenia,[11] which in turn has been linked to a dysfunctional dopamine system. Ketamine is known to induce cortical release of dopamine[16] and D2 dopamine receptor antagonists ameliorate ketamine-induced prefrontal cortical impairment in rats.[18] Like ketamine, nitrous oxide also causes dopamine metabolic changes in the cortex of rats which is seen as an increase of 3,4-dihydroxyphenylalanine, the major metabolite of dopamine in the rat brain;[15] we recently confirmed this finding in a tissue culture preparation.[33] In contrast, xenon does not increase dopamine release in PC12 cells.[19] It is noteworthy that, of the neurotransmitters in cortical afferent neurones, only dopamine is distributed to frontal and cingulate areas.[34] All of the above argue for a possible role of dopamine in the neurotoxic effects of NMDA receptor antagonists. The data presented here (Fig. 5), showing that the dopamine D2 receptor antagonist haloperidol blocks the toxicity produced by both nitrous oxide and ketamine, provides supporting evidence for this view.

Possible clinical implications

Xenon, when used as a general anaesthetic, has virtually no side-effects[28 29] and rapidly distributes into the CNS when breathed. Its ability to act as a neuroprotectant together with its apparent lack of neurotoxicity sets xenon apart from other anaesthetics, such as nitrous oxide and ketamine, with known NMDA antagonist properties. Thus, xenon might be considered as the anaesthetic of choice when neuroneal injury can be anticipated, for example in cardiac surgery requiring coronary artery bypass.[35]

Acknowledgements

This work was supported by grants from the Medical Research Council, London, UK, and from the Chelsea and Westminster NHS Healthcare Trust. Dr Wilhelm was the recipient of a research stipend from the Deutsche Forschungsgemeinschaft. We thank Dr Vesna Jevtovic-Todorovic for helpul guidance on the experimental procedure.

References

1 Olney JW. Brain lesions, obesity, and other disturbances in mice treated with monosodium glutamate. *Science* 1969; **164**: 719–21

2 Choi DW, Koh JY, Peters S. Pharmacology of glutamate neurotoxicity in cortical cell culture: attenuation by NMDA antagonists. *J Neurosci* 1988; **8**: 185–96

3 Sarraf-Yazdi S, Sheng H, Miura Y, *et al.* Relative neuroprotective effects of dizocilpine and isoflurane during focal cerebral ischemia in the rat. *Anesth Analg* 1998; **87**: 72–8

4 Harada H, Kelly PJ, Cole DJ, Drummond JC, Patel PM Isoflurane reduces N-methyl-D-aspartate toxicity *in vivo* in the rat cerebral cortex. *Anesth Analg* 1999; **89**: 1442–7

5 Popovic R, Liniger R, Bickler PE. Anesthetics and mild hypothermia similarly prevent hippocampal neurone death in an *in vitro* model of cerebral ischemia. *Anesthesiology* 2000, **92**: 1343–9

6 Kudo M, Aono M, Lee Y, Massey G, Pearlstein RD, Warner DS Effects of volatile anesthetics on *N*-methyl-D-aspartate excitotoxicity in primary rat neuroneal-glial cultures. *Anesthesiology* 2001; **95**: 756–65

7 Arrowsmith JE, Harrison MJ, Newman SP, Stygall J, Timberlake N, Pugsley WB. Neuroprotection of the brain during cardiopulmonary bypass: a randomized trial of remacemide during coronary artery bypass in 171 patients. *Stroke* 1998; **29**: 2357–62

8 Franks NP, Dickinson R, de Sousa SLM, Hall AC, Lieb WR. How does xenon produce anaesthesia? *Nature* 1998; **396**: 324

9 de Sousa SL, Dickinson R, Lieb WR, Franks NP. Contrasting synaptic actions of the inhalational general anesthetics isoflurane and xenon. *Anesthesiology* 2000; **92**: 1055–66

10 Anis NA, Berry SC, Burton NR, Lodge D. The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neuronees by *N*-methyl-aspartate. *Br J Pharmacol* 1983; **79**. 565–75

11 Malhotra AK, Pinals DA, Weingartner H, *et al.* NMDA receptor function and human cognition: the effects of ketamine in healthy volunteers. *Neuropsychopharmacology* 1996; **14**: 301–7

12 Olney JW, Labruyere J, Price MT. Pathological changes induced in cerebrocortical neurones by phencyclidine and related drugs. *Science* 1989; **244**: 1360–2

13 Allen HL, Iversen LL. Phencyclidine, dizocilpine, and cerebrocortical neurones. *Science* 1990; **247**: 221

14 Jevtovic-Todorovic V, Todorovic SM, Mennerick S, *et al.* Nitrous oxide (laughing gas) is an NMDA antagonist, neuroprotectant and neurotoxin. *Nature Med* 1998; **4**: 460–3

15 Murakawa M, Adachi T, Nakao S, Seo N, Shingu K, Mori K. Activation of the cortical and medullary dopaminergic systems by nitrous oxide in rats: a possible neurochemical basis for psychotropic effects and postanesthetic nausea and vomiting *Anesth Analg* 1994; **78**: 376–81

16 Moghaddam B, Adams B, Verma A, Daly D. Activation of glutamatergic neurotransmission by ketamine: a novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. *J Neurosci* 1997; **17**: 2921–7

17 Lindefors N, Barati S, O'Connor WT Differential effects of single and repeated ketamine administration on dopamine, serotonin and GABA transmission in rat medial prefrontal cortex. *Brain Res* 1997; **759**: 205–12

18 Verma A, Moghaddam B. NMDA receptor antagonists impair prefrontal cortex function as assessed via spatial delayed alternation performance in rats: modulation by dopamine. *J Neurosci* 1996; **16**: 373–9

19 Petzelt CH. New concepts in neuroprotection. *J Anasth Intensivbehandlung* 2001; **3**: S38

20 MacDonald MC, Robertson HA, Wilkinson M. Expression of c-fos protein by *N*-methyl-D-aspartic acid in hypothalamus of immature female rats: blockade by MK-801 or neonatal treatment with monosodium glutamate. *Brain Res Dev* 1990; **56**: 294–7

21 Uemura Y, Kowall NW, Moskowitz MA. Focal ischemia in rats causes time-dependent expression of c-fos protein immunoreactivity in widespread regions of ipsilateral cortex. *Brain Res* 1991; **552**: 99–105

22 Gass P, Herdegen T, Bravo R, Kiessling M. Induction and suppression of immediate early genes in specific rat brain regions by the non-competitive *N*-methyl-D-aspartate receptor antagonist MK-801. *Neuroscience* 1993; **53**: 749–58

23 Walton M, MacGibbon G, Young D, *et al.* Do c-Jun, c-Fos, and amyloid precursor protein play a role in neuroneal death or survival? *J Neurosci Res* 1998; **53**: 330–42

24 Zhai QZ, Traub RJ. The NMDA receptor antagonist MK-801 attenuates c-Fos expression in the lumbosacral spinal cord following repetitive noxious and non-noxious colorectal distention. *Pain* 1999; **83**: 321–9

25 Jevtovic-Todorovic V, Wozniak DF, Benshoff ND, Olney JW. A comparative evaluation of the neurotoxic properties of ketamine and nitrous oxide. *Brain Res* 2001; **895**: 264–7

26 Hasegawa K, Litt L, Espanol MT, Sharp FR, Chan PH. Expression of c-fos and hsp70 mRNA in neonatal rat cerebrocortical slices during NMDA-induced necrosis and apoptosis. *Brain Res* 1998; **785**: 262–78

27 Sharp FR, Butman M, Aardalen K, *et al.* neuroneal injury produced by NMDA antagonists can be detected using heat shock proteins and can be blocked with antipsychotics. *Psychopharmacol Bull* 1994; **30**: 555–60

28 Luttropp HH, Thomasson R, Dahm S, Persson J, Werner O. Clinical experience with minimal flow xenon anesthesia. *Acta Anaesthesiol Scand* 1994; **38**: 121–5

29 Lynch C, 3rd, Baum J, Tenbrinck R. Xenon anesthesia. *Anesthesiology* 2000; **92**: 865–8

30 Loscher W, Honack D. The behavioural effects of MK-801 in rats: involvement of dopaminergic, serotonergic and noradrenergic systems. *Eur J Pharmacol* 1992; **215**: 199–208

31 Nishizawa N, Nakao S, Nagata A, Hirose T, Masuzawa M, Shingu K. The effect of ketamine isomers on both mice behavioral responses and c- Fos expression in the posterior cingulate and retrosplenial cortices. *Brain Res* 2000; **857**: 188–92

32 Nagata A, Nakao Si S, Nishizawa N, *et al.* Xenon inhibits but N_2O enhances ketamine-induced c-Fos expression in the rat posterior cingulate and retrosplenial cortices. *Anesth Analg* 2001; **92**: 362–8

33 Inomata S, Maze M, Hashimoto T, Jones M, Fujinaga M. Nitrous oxide induced met-enkephalin release provokes dopamine release in rat adrenal medulla cultured *in vitro*. *Anesthesiology* 2000; **93** (Suppl): A758

34 Jones EG. Neurotransmitters in the cerebral cortex. *J Neurosurg* 1986; **65**: 135–53

35 Newman MF, Kirchner JL, Phillips-Bute B, *et al.* Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. *N Engl J Med* 2001; **344**: 395–402

British Journal of Anaesthesia 89 (5). 747–59 (2002)

BJA

REVIEW ARTICLE

Preoperative evaluation of patients with, or at risk of, coronary artery disease undergoing non-cardiac surgery

P.-G. Chassot[1], A. Delabays[2] and D. R. Spahn[3]*

[1]Department of Anaesthesiology, [2]Division of Cardiology and [3]Department of Anaesthesiology, University Hospital Lausanne (CHUV), CH-1011 Lausanne, Switzerland.

**Corresponding author*

The increasing number of patients with coronary artery disease undergoing major non-cardiac surgery justifies guidelines concerning preoperative evaluation, stress testing, coronary angiography, and revascularization. A review of the recent literature shows that stress testing should be limited to patients with suspicion of a myocardium at risk of ischaemia, and coronary angiography to situations where revascularization can improve long-term survival. Recent data have shown that any event in the coronary circulation, be it new ischaemia, infarction, or revascularization, induces a high-risk period of 6 weeks, and an intermediate-risk period of 3 months. A 3-month minimum delay is therefore indicated before performing non-cardiac surgery after myocardial infarction or revascularization. However, this delay may be too long if an urgent surgical procedure is requested, as for instance with rapidly spreading tumours, impending aneurysm rupture, infections requiring drainage, or bone fractures. It is then appropriate to use perioperative beta-block, which reduces the cardiac complication rate in patients with, or at risk of, coronary artery disease. The objective of this review is to offer a comprehensive algorithm to help clinicians in the preoperative assessment of patients undergoing non-cardiac surgery.

Br J Anaesth 2002; **89**: 747–59

Keywords: heart, coronary artery disease; surgery, non-cardiac; surgery, preoperative assessment

Accepted for publication: April 8, 2002

Contemporary medicine shows a trend towards more aggressive surgery in sicker patients, among whom the prevalence of ischaemic heart disease is increasing. This tendency creates a requirement for guidance in the preoperative evaluation of patients known to have, or at risk of, coronary artery disease. There is an abundance of studies on this subject, but the way to evaluate these patients is still the object of considerable debate. Much of the controversy is because of the obvious difficulties of conducting large randomized controlled clinical trials on this topic, and to the relatively low incidence of perioperative cardiac events (<10%). The rate of postoperative myocardial infarction is 0.7% after general surgery in a male population over 50 yr old, but increases to 3.1% after vascular surgery where the prevalence of asymptomatic coronary artery disease is particularly high.[3 53 61] Because of this prevalence, most of the studies have focused on vascular patients, who represent less than 10% of the adult surgical population. This fact may introduce a bias when the results are extrapolated to other surgical cohorts

The purpose of preoperative evaluation is to lower perioperative morbidity and mortality with minimal expense from preoperative testing, and to concentrate economic investment on high-risk patients where specialized tests might modify perioperative management and improve long-term benefit. Testing a low-risk population not only increases costs unnecessarily, but may increase morbidity and causes harm by delaying a non-cardiac operation. The main question to be answered is: does the patient need cardiological testing? When coronary artery disease is present, three other questions arise: may the patient benefit from coronary revascularization? Is non-cardiac surgery so imperative that it should be carried out rapidly despite the risk? Is it possible to decrease this risk?

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

As the workload resulting from perioperative ischaemic cardiac evaluation is significant, clinicians need practical guidelines for their daily practice. This review aims to offer them an update on the literature on preoperative assessment of patients known to have, or at risk of, coronary artery disease undergoing non-cardiac surgery. It also presents an evaluation algorithm used in our institution. The level of evidence in the studies cited in the text is mentioned in the references.

Clinical predictors

Despite sophisticated technologies, history and physical examination of the patient remain the key elements of preoperative risk assessment. Risk stratification of patients with known, or at risk of, coronary artery disease is usually based on three elements:[115] (i) the patient risk factors; (ii) functional capacity of the patient; and (iii) the risk factors of surgery.[20] The vast majority of the studies has been performed in North America and among Veterans Administration Hospitals, the population of which consists mainly of elderly white male patients. However, the prevalence of coronary artery disease and its morbidity varies considerably in different countries. For example, the incidence of infarction among patients with abdominal aortic aneurysm is 16% in France, but 50% in Sweden.[4 55] Similarly, there are ethnic differences in the response to treatment between white and non-white populations.[24 124] Thus, it may be inaccurate to transpose the results of one population to another. On the other hand, the risk of surgery is highly dependent on surgical skills, anaesthetic care, and nursing quality. Each institution should therefore establish its own audit in order to take appropriate decisions when choices have to be made between different treatment modalities.

Risk factors of the patients

Risk factors of the patients are usually subdivided into three categories: major, intermediate, and minor (Table 1). Major predictors are markers of unstable coronary disease and include: recent myocardial infarction (<6 weeks), unstable or severe angina (class III–IV), ongoing ischaemia after myocardial infarction, ischaemia and congestive heart failure, or malignant arrhythmias. New or changing symptoms suggest atheromatous plaque rupture and should be presumed to be infarction unless proven otherwise. A 6-week period is necessary for the myocardium to heal after an infarction and for the thrombosis to resolve.[116] Patients with coronary revascularization done within the preceding 40 days should also be classified as high-risk patients.[79] Because of sympathetic stimulation and hypercoagulability during and after surgery, patients with major predictors have a five times greater perioperative risk.[20 84] Only vital or emergency surgical procedures should therefore be considered for these patients. All elective operations should be postponed and the patients properly investigated and treated.

Table 1 Classification of cardiac risk factors linked to patient status modified from references.[20 22 54 69 83 92 114] CABG=coronary artery bypass graft

---

Major factors (markers of unstable coronary artery disease)
Myocardial infarction <6 weeks
Angina class III–IV
Residual ischaemia after myocardial infarction
Clinical ischaemia and congestive heart failure
Clinical ischaemia and malignant arrhythmias
CABG or PTCA <6 weeks

Intermediate factors (markers of stable coronary disease)
Prior myocardial infarction >6 weeks and <3 months (>3 months if complicated) by clinical history or ECG abnormalities
Angina class I–II
Asymptomatic patient post infarction with maximal therapy
Documented previous perioperative ischaemia
Silent ischaemia (Holter monitoring)
Post CABG or PTCA >6 weeks and <3 months, or >6 yr, or with anti-anginal therapy
Ventricular arrhythmia
Diabetes mellitus
Age (physiological) >70 yr
Compensated or prior heart failure, ejection fraction <0.35

Minor factors (increased probability of coronary artery disease)
Familial history of coronary artery disease
Polyvascular status
Uncontrolled systemic hypertension
Hypercholesterolaemia
Smoking
ECG abnormalities (arrhythmia, LVH, bundle branch block)
Post infarction (>3 months), asymptomatic without treatment
Post CABG or PTCA >3 months and <6 yr, and no symptoms of angina nor anti-anginal therapy

Intermediate-risk factors, such as previous myocardial infarction (>6 weeks and <3 months) without sequelae or threatened myocardium, stable angina (class I–II) with optimal medical treatment, or documented previous perioperative ischaemic events, are independent predictors for perioperative cardiac complications; they are proof of well established but controlled coronary artery disease. Diabetes mellitus is included in this category because it is frequently associated with silent ischaemia, and represents an independent risk factor for perioperative mortality, as do low ejection fraction (EF <0.35) and compensated heart failure.[20 65] The relevance of advanced age (>70 yr), hypertension and left ventricular hypertrophy (LVH) to the intermediate or minor risk category is still controversial. American guidelines tend to consider age as a minor factor but, if it is estimated by physiological age and not chronological age, it should belong to the intermediate category.[20 22 50 65 93 101] The presence of hypertension among intermediate or minor risk categories depends probably on the population studied, as it is an easily controllable factor in the perioperative period.[57] LVH has been considered as an independent marker of ischaemic disease and cardiac complications, but recent recommendations tend to consider it a minor factor.[17 33 37 65 76] Risk

Table 2 MET in increasing order (Duke Activity Status Index) (adapted from Hlatky, 1989[54])

1–4 MET	Standard light home activities Walk around the house Walk 1–2 blocks on level ground at 3–5 km h^{-1}
5–9 MET	Climb a flight of stairs, walk up a hill Walk on level ground at >6 km h^{-1} Run a short distance Moderate activities (golf, dancing, mountain walk)
>10 MET	Strenuous sports (swimming, tennis, bicycle) Heavy professional work

Table 3 Cardiac risk classification of non-cardiac surgical procedures adapted from ACA/AHA guidelines for perioperative cardiovascular evaluation for non-cardiac surgery[20, 22]

Minor procedures (cardiac complication rate <1%)
Endoscopic procedures
Ambulatory surgery
Breast and superficial procedures
Eye surgery
Plastic and reconstructive surgery
Intermediate procedures (cardiac complication rate 1–5%)
Minor vascular surgery, including carotid endarterectomy
Abdominal and thoracic procedures
Neurosurgery
ENT procedures
Orthopaedic surgery
Prostatectomy
Major procedures (cardiac complication rate >5%)
Emergency intermediate and major procedures
Aortic and major vascular surgery
Prolonged surgical procedures, large fluid shifts or blood loss
Unstable haemodynamic situations

factors are additive: complication rates increase with their number, as does the necessity to investigate the patients.[65, 76]

Minor risk factors are markers of an increased probability of coronary artery disease, but not of an increased perioperative risk; they are mentioned in Table 1.[2] In patients asymptomatic within 6 yr after coronary artery bypass grafting (CABG) or percutaneous transluminal coronary angioplasty (PTCA), evidence suggests that the risk of subsequent non-cardiac surgery is the same as in non-coronary patients, as long as the delay of 3 months is respected after revascularization, and the stress tests are negative within the previous 2 yr.[21, 22, 26, 37, 85, 111]

Functional capacity

Exercise tolerance is a major determinant of perioperative risk.[20, 22, 42, 81] It is usually evaluated by the estimated energy requirement for various activities, and graded in metabolic equivalents (MET) on a scale defined by the Duke Activity Status Index (Table 2).[54] One MET represents the oxygen consumption of a resting adult (3.5 ml kg^{-1} min^{-1}). Ergometric measurements on a treadmill inducing ischaemia at low-level exercise (<5 MET or heart rate <100 min^{-1}) identifies a high-risk group, whereas the achievement of more than 7 MET (or heart rate >130 min^{-1}) without ischaemia identifies a low-risk group.[122] Vascular patients who are able to exercise to 85% of their maximal heart rate have a low risk of a perioperative cardiac event.[78] More simply, the inability to climb two flights of stairs is associated with a positive predictive value of 89% for cardiopulmonary complications.[42] In the absence of valve pathology, the ejection fraction of the left ventricle can be considered as an adequate measurement of the myocardial functional reserve.[100] Patients with good functional capacity and no symptoms can be considered free of any severe coronary artery disease.[86] Despite its predictive value in the perioperative setting, the Duke Activity Status Index has never been specifically tested for ischaemic patients.[84]

Risk factors associated with surgery

Surgical procedures can be stratified into three categories, according to their level of perioperative physiological stress (Table 3).[20, 22] When estimating the risk of an operation, one must also take into consideration the risk of not operating on the patient. This evaluation is particularly important for oncological or limb salvaging procedures. It is unethical to reject a patient when their survival is threatened by the disease—as with rapidly spreading tumours, impending aneurysm rupture, infections requiring surgery, or disabling bone fractures. In order to balance the risks, it might be necessary to limit the extent of the planned procedure, or to plan repeated operations. Risk reduction strategies must also be applied, such as maintaining normothermia, avoiding extreme anaemia, controlling postoperative pain, and prescribing perioperative beta-block.[76, 107, 127] The performance of the individual institution must be taken into account, as it is a determinant factor in the success of particular procedures.

Previous ischaemia

During the 1980s, the rule prevailed to wait 6 months after a myocardial infarction before embarking on non-cardiac surgery.[97, 109, 114] Since then, the cardiological management and the functional assessment of patients have evolved significantly. It appears now that the risk after a previous infarction is related less to the age of the infarction than to the functional status of the ventricles and to the amount of myocardium at risk from further ischaemia, as evaluated during convalescence.[22, 104, 105] A small infarction without residual angina in the context of a good functional status allows essential non-cardiac surgery as soon as 6 weeks after the ischaemic episode.[115] On the contrary, a patient with a large infarct, residual symptoms and ejection fraction below 0.35 has a high probability of a further cardiac event, even 6 months after the infarction. Usual practice guidelines consider the period within 6 weeks of infarction as a time of high risk for a perioperative cardiac event, because it is the mean healing time of the infarct-related lesion.[22 80 116] The period from 6 weeks to 3 months is of intermediate risk; this period is extended beyond 3 months in cases with complications such as arrhythmias, ventricular dysfunction, or continued medical therapy.[1] In uncomplicated cases, no benefit can be demonstrated for delaying surgery more than 3 months after an ischaemic accident.[115]

Previous coronary revascularization

Patients who do well after CABG have an attenuated risk of cardiac events during subsequent non-cardiac surgery. Retrospective studies have disclosed a significant improvement in survival of revascularized patients, particularly those with triple-vessel coronary artery disease and depressed ventricular function, when they undergo subsequent non-cardiac vascular surgery.[85 98 110] In the Coronary Artery Surgery Study (CASS) experience, these patients have a mortality of 0.9%, instead of 2.4% for those who have not been revascularized;[37] recent data show the same trend.[51] However, when the complication and mortality rates of CABG are taken into account, the combined mortality of cardiac and non-cardiac procedures is not different from the mortality of non-cardiac surgery when ischaemic heart disease has been managed by medical treatment only.[37] A patient might therefore benefit from preoperative coronary revascularization if the CABG procedure presents a low risk and will improve long-term survival, and if the planned non-cardiac procedure is high risk but can wait for at least 3 months.

The short-term effect of prophylactic CABG among vascular patients has been addressed in two decisional analyses; both showed it was safer to proceed directly with a non-cardiac operation and close monitoring before coronary revascularization.[31 75] The benefit of coronary revascularization might be even lower among patients undergoing non-vascular surgery, as they have already a lower probability of perioperative cardiac events.[3 84] Obviously, there is no indication to advise prophylactic revascularization in order to protect the ischaemic myocardium from the effects of a subsequent non-cardiac operation. The indications for coronary revascularization are aimed at reducing long-term mortality and prolonging survival.[33 36 75] They are the same in patients being evaluated for a non-cardiac operation as for non-surgical population and include: unstable angina, left main coronary artery disease, three-vessel disease, proximal left anterior descending artery disease, and decreased ventricular function.

Asymptomatic, functionally active patients with previous successful coronary revascularization within the last 6 yr are in a low-risk category and should not be investigated further for a non-cardiac operation; this cut-off point is based on a slight but non-significant increase in postoperative infarction rate among patients 6 yr after CABG surgery.[21] Patients having a negative stress test or satisfactory angiography in the last 2 yr can be cleared for non-cardiac surgery without further testing, if the symptomatology and treatment have not changed since the examination.[20 22]

In the 1990s, it seemed that PTCA had a significant protective effect on the ischaemic complications of subsequent non-cardiac surgery. In two studies from the Mayo Clinic, major vascular surgery was performed on average 11 days after PTCA;[27 58] overall mortality of surgery was halved and infarction rate five times less in the groups having previous PTCA compared with non-revascularized patients. Such results with dilatative angioplasty have been repeated, showing improvement in vascular surgery outcome for patients having undergone PTCA 11 days to 18 months earlier.[45] However, with the advent of stenting during PTCA, recent studies have heralded fundamentally different results. In one study, there were eight deaths and seven myocardial infarctions among 40 patients who underwent coronary stent placement less than 2 weeks before non-cardiac surgery.[60] In addition, patients undergoing non-cardiac surgery within 40 days of PTCA are nearly three times more likely to have an adverse cardiac event than normal controls, and are no less likely to have a poor cardiac outcome than non-revascularized patients until 90 days after PTCA.[92] Any surgery performed within 6 weeks of PTCA presents an excessive risk of stent thrombosis and infarction if the antiplatelet medication is stopped, or of major bleeding if the treatment is maintained throughout the operation.[22 79 119] This is a period of major risk: most of the re-stenoses requiring repeat PTCA occur during the first months after stenting, and documented stent thrombosis is associated with a mortality rate of 7%.[15 17] The optimal timing for surgery is therefore a delay of 3 months after PTCA and stenting. Compared with PTCA, CABG with internal mammary grafting has a better long-term protective effect, particularly in diabetic patients;[38] the rate of late cardiac events (>3 yr) is halved in surgically revascularized patients.[27 35]

Preoperative testing

Preoperative testing is aimed at answering precise questions raised by clinical history and examination. No cardiovascular test should be performed if the results will not change perioperative management. The therapeutic impact may differ according to the situation: medical treatment may be optimized, surgical procedure modified, anaesthetic management adjusted, or the risk/benefit ratio of a surgical procedure evaluated differently. These complex decisions can be taken more objectively when the actual risk can be quantified by appropriate screening tests.[70] However, no magic test will ever exist to fully stratify all risks, because perioperative cardiac events are multifactorial.[84]

The indication for preoperative tests is based on Bayes' theorem, which specifies that the predictive value of testing is optimized when it is applied to an intermediate-risk population (Table 1), as the incidence of false negatives and false positives is inversely proportional to disease

Table 4 Comparison of three preoperative stress tests. *Relative risk is the probability of a cardiac event when a test result is positive divided by the probability of that event when the test result is negative (modified from Mantha[73]) **Cost at the University Hospital of Lausanne (CHUV), Switzerland

Test	Median relative risk*	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Cost** (€)
Ambulatory ECG (Holter)	2 7	68	66	25	190
Exercise ECG		69	73	20	220
Dipyridamole-thallium	4 6	85	80	23	410
DSE 6.2	80	90	30	570	

prevalence. The probability of a complication is a function of the probability of the disease in the category to which the patient belongs. In such a Bayesian model using clinical predictors and results of dipyridamole-thallium scintigraphy (DTS), it appears that modifications are introduced by the test only in the intermediate-risk patient category.[66] Without symptoms of angina, previous infarction or heart failure, the probability of suffering from coronary artery disease is 6%; if diabetes is also excluded, the probability falls to 4%;[86] further testing of such a patient has an extremely low impact on complication rate. Similarly, the outcome of a patient with a clear history of active coronary artery disease will not be modified by screening tests.

Stress tests (exercise ECG, DTS, or dobutamine echocardiography) are dynamic investigations, which demonstrate the ischaemic threshold, the maximal tolerated heart rate, the localization, and the amount of threatened myocardium. An interruption of the test before reaching the maximal theoretical heart rate identifies an increased risk of perioperative ischaemic events.[70] The positive predictive value of all stress tests is modest (20–30%), whereas their negative predictive value is excellent (95–100%); this should not be surprising, as the incidence of perioperative cardiac complications is low (<10%) and more than 90% of patients have a straightforward perioperative course.[10] In a meta-analysis of the predictive value of four preoperative tests (DTS, ejection fraction estimated by radionuclide ventriculography, ambulatory electrocardiography, and dobutamine stress echocardiography (DSE)), DSE appears more discriminating, but the data do not allow selection of an optimal test because of overlapping confidence intervals (Table 4).[73] DSE seems particularly informative because it investigates the segmental coronary blood supply and allows simultaneous quantification of ventricular function.

The pertinence of tests is increased for multi-vessel disease, but diminished in cases of isolated single-vessel stenosis.[41] Beside the specificities of each test, it is the expertise of its medical interpretation and the characteristics of the population in which it is applied which alters its impact. Such differences may introduce significant bias when comparing the efficiency of these tests in predicting outcomes. The comparison of various studies is further confounded because some are based on consecutive case recruitment, whereas others analyse selective testing of classes of patients.[33]

Electrocardiography (24 h Holter monitoring)

Preoperative ambulatory ECG (Holter monitoring) is relatively inexpensive but may be difficult to analyse because of electrocardiographic abnormalities precluding adequate interpretation in up to 50% of patients.[95] One highly powered study demonstrated that the detection of silent preoperative ischaemia has a positive predictive value of 38% for postoperative cardiac events, whereas its absence precludes perioperative problems in non-vascular surgery in 99% of patients and in vascular surgery in 86%.[30] When electrocardiographic criteria of LVH were added to ST segment depression, the preoperative Holter ECG became significantly predictive of postoperative events.[62] However, other studies show less clear-cut data, and results are not unanimous in non-cardiac surgery, probably because postoperative ischaemia is primarily a result of ischaemic events occurring during surgery.[67,69,95] Perioperative stress and techniques of patient management are probably more determinant features than the presence of preoperative electrocardiographic signs of ischaemia.

Exercise ECG

The exercise ECG is a widely available and inexpensive method of screening for coronary artery disease but depends on the exercising ability of the patient and the legibility of the ECG. Often, vascular patients do not reach the target heart rates because of limb claudication, and therefore have an inadequate examination. In patients who can perform the test, studies conducted in vascular and non-vascular patients are not conclusive for its ability to predict perioperative cardiac complications.[32,41,59,113] However, a recent prospective study on intermediate-risk patients confirmed that a ST-segment depression of 0.1 mV or more during exercise is an independent predictor of perioperative ischaemic events.[39] Because of its availability and low cost, the exercise ECG should be considered as the first screening step in stress testing for non-vascular patients with a normal ECG and good mobility.[20]

Dipyridamole-thallium scintigraphy

When myocardial perfusion is increased by vasodilation with dipyridamole, infarcted areas appear as fixed defects, whereas ischaemic myocardium appears as defects, which are reversible when reperfused on later images. There is an incremental increase in the probability of postoperative cardiac events with increasing size and number of these defects.[12 14] Reversible defects are efficient markers of the myocardium at risk, and are clearly associated with an adverse cardiac event.[19] Quantification of their delayed redistribution at 4–24 h is more predictive of cardiac death or myocardial infarction than simple dichotomous interpretation in positive/negative results.[32 108 118] There is strong evidence that DTS has a good predictive value for determining a low or high operative risk when applied to a selected population of clinical intermediate-risk, vascular patients.[66 118] However, it has no real screening value, when applied to a large unselected vascular or non-vascular population, or among patients already classified clinically as low- or high-risk candidates for surgery.[4 68]

Left ventricular ejection fraction

There is strong evidence that simple assessment of the resting ejection fraction by transthoracic echocardiography alone does not improve prediction of ischaemic complications in cardiac patients, although it is useful for evaluating outcome in current or poorly controlled heart failure.[22 49 77] A depressed ejection fraction predicts only postoperative left ventricular dysfunction and correlates better with late than early postoperative cardiac events.[83 102] Technetium-99 radionuclide angiography offers a more precise and more reproducible measurement, but is not a better predictor of ischaemic events.[117]

Dobutamine stress echocardiography

An increase in oxygen demand following dobutamine perfusion (40 $\mu g\ kg^{-1}\ min^{-1}$) is more discriminative, as it can induce wall motion abnormalities pathognomonic of ischaemic myocardium. According to most meta-analyses, it offers the best prediction for perioperative events, with a negative predictive value close to 100% and a positive predictive value up to 38% among intermediate- or high-risk patients (Table 4), even if it does not add discriminative power in patients with no clinical markers of coronary artery disease.[11 23 74 84 88 108] Patients demonstrating extensive ischaemia under dobutamine stimulation (>5/16 left ventricular segments involved), experience 10 times more cardiac events than patients with limited stress-induced ischaemia (<4 segments involved).[11] Based on a Dutch study of 1351 consecutive patients undergoing major vascular surgery, DSE can be considered as an effective test for identifying the small group (2%) of patients at high ischaemic risk who should undergo coronary angiogram and possible revascularization. In contrast, patients with moderate risk (<4 segments involved) could undergo surgery directly under beta-block protection.[11]

Coronary angiography

Coronary angiography is an invasive procedure, which carries mortality of 0.01–0.05%, and a morbidity of 0.03–0.25%.[75] It is indicated only in cases of unstable coronary syndromes, of uncertain stress tests in high-risk patients undergoing major surgery, or when there is a possible indication for coronary revascularization.[22] When the coronary artery disease is diffuse in small vessels, as in subendocardial ischaemia without wall motion abnormalities, or when the patient is not a candidate for revascularization because of comorbid states, coronary angiography has little impact, as the probability of the results leading to PTCA or CABG is very low.[104] Coronary angiography should therefore be performed before a non-cardiac operation only in high-risk patients who warrant coronary revascularization for medical reasons, irrespective of the preoperative context.

Test limitations

Predictions are only probabilities of events: a negative preoperative test in a particular patient, although reassuring for the anaesthetist, does not mean that cardiac complications are excluded. Independent of its prognostic capacity, each test has its own advantages and contraindications (Table 5). More importantly, the primary factor for deciding the most efficient test is institution-specific: the best prediction will be provided by the most qualified department, whether it is cardiology, nuclear medicine, or the echo laboratory.

The concept that postoperative ischaemia and infarction are related to perioperative excess oxygen demand is supported by the fact that ischaemic events peak at the second and third postoperative day, whereas tachycardia is maximum during days 1 and 2.[69] Patients with higher maximum heart rates after surgery have more ischaemic episodes and a longer cumulative duration of ischaemia.[96] There is a strong correlation between immediate postoperative ischaemia (ST-segment depression) and cardiac events supervening after surgery.[67] Nowadays, stress echocardiography is the closest replication of an equivalent increase in myocardial oxygen consumption. Nevertheless, there is no test that adequately mimics the physiological stress response to surgery, with prolonged sympathetic stimulation and tachycardia, increased coronary vasomotor tone, hypercoagulability, potential atheromatous plaque rupture leading to thrombus formation, hypothermia, and blood loss.[28 33 107] Moreover, the culprit lesion causing myocardial infarction often occurs in a insignificantly stenosed coronary vessel.[26 43] Although DTS and DSE have good predictive accuracy in patients undergoing vascular surgery,[87 88] they seem not as efficient in patients undergoing non-vascular operations.[63 125] Without prospective studies on selected populations, it is not yet

Table 5 Advantages and disadvantages of preoperative tests

Test	Advantages	Disadvantages
Tests for myocardial perfusion		
Ambulatory ECG (Holter)	Simple, non-invasive	Baseline ECG abnormalities restrict diagnostic possibilities, poor predictive ability
Exercise ECG	Simple, non-invasive	Relies on patient mobility, baseline ECG abnormalities restrict diagnostic possibilities, poor predictability in vascular patients
DTS	Sensitivity 85%, specificity 80%	Contraindicated in unstable angina and asthma, delayed images at 4 to 24 h use of radioactive material, requires overnight fasting
DSE	Sensitivity 80%, specificity 90%, ventricular function detects dynamic ischaemia	Depends on transthoracic echogenicity, operator-dependent
Tests for myocardial function		
Transthoracic echo	Simple, rapidly available	Diagnostic only in case of transmural ischaemia, no predictability for ischaemia
Technetium-99 scanning	No interobserver variability, high reproductibility	Expensive, less availability

possible to define the real impact of stress tests on outcome in general surgery.

Patients receiving effective chronic beta-block are difficult to evaluate with stress tests because they have a limited increase in heart rate and cardiac output on exercise. The sensitivity of stress tests for diagnosing a coronary lesion is significantly lowered under these circumstances.[29 123] However, as a preoperative prognostic tool, these tests retain their full value, as they demonstrate which level of stress these patients can endure before showing myocardial ischaemia under the protection of beta-adrenergic antagonism. The decreased incidence of ischaemic modifications with beta-block is a diagnostic drawback, but is nevertheless a demonstration of the level of protection reached with this medication.

Testing takes time and money. Only intermediate-risk (Table 1), and low-functional status (Table 2) patients, undergoing major or vascular surgery (Table 3) benefit from stress testing. High-risk patients should undergo coronary angiography. In a theoretical model of decision analysis, using as an end-point mortality rates for abdominal aortic aneurysm resection and CABG, Glance[44] suggests that preoperative screening, in which high-risk patients proceed directly to angiography and possible CABG, intermediate-risk patients are first screened with DTS, and low-risk patients undergo no testing before vascular surgery, may improve 5-yr survival from 77 to 86%. In this model, routine testing of all patients is of no benefit compared with selective testing of the intermediate-risk category, and is more expensive. Some patients have an obvious indication for urgent surgery and yet have a clinical coronary status, which would require investigation because of the possible need for revascularization. Testing and treating them would impose an unacceptable delay in the surgical treatment of the life-threatening primary disease. In such a case, it is not indicated to thoroughly investigate the patient, as the decision to operate with the shortest delay is made whatever the results. Based on recent data on risk stratification, it can be asserted that these emergency operations can be performed as soon as possible, but should be accompanied by perioperative treatment with beta-blockers.[11 90 127]

Diabetes mellitus

In diabetic patients, the risk of coronary artery disease is two to four times higher than in the corresponding general population.[2] Moreover, diabetes is frequently associated with silent ischaemia; if detected by Holter monitoring, it has a positive predictive value of 35% for postoperative cardiac events.[30] Asymptomatic diabetic patients have an incidence of ischaemic events similar to patients with stable coronary artery disease.[48] Clinicians should have a low threshold for cardiac testing in diabetics, as the following factors must be added to the usual minor clinical predictors (Table 1): obesity, physical inactivity, albuminuria, dyslipidaemia, and age more than 55 yr.[103] Chronically elevated glucose (>11 mmol litre^{-1}) and glycosylated haemoglobin levels greater than 7% are better predictors of cardiac events than the simple presence of diabetes.[16 47 103] Diabetics with proven coronary artery disease (intermediate-risk predictors) have a much poorer long-term outcome after vascular surgery, with an increased probability of cardiac death or myocardial infarction compared with non-diabetics with equivalent coronary artery disease.[12 14]

Asymptomatic diabetic patients with two or more risk factors should be investigated by stress testing if they have a low-functional capacity (Table 2), or if they are to undergo major or vascular surgery. Only individuals with good functional capacity undergoing minor or intermediate surgery (Table 3) can proceed directly to surgery. This is a more aggressive attitude than for the general population. The modification of hypoglycaemic symptoms with beta-blockers does not preclude their use in diabetics, as they offer a perioperative protection against ischaemia.[47 127]

Vascular surgery

Preoperative evaluation for coronary ischaemia most frequently involves vascular surgical patients, even if they are asymptomatic because of limitations in physical activity: 37% of surgical vascular patients without symptoms of myocardial ischaemia have significant coronary disease at angiography, and 15% have disease that warrants intervention.[1 52 53] The perioperative infarction rate in vascular surgery is three times higher than in non-vascular surgery.[61] The mortality rate for non-cardiac vascular surgery in patients with coronary artery disease is 5–9%, whereas it is only 1–2% in patients free of coronary disease, or in patients who have had previous CABG.[37 40 53] The incidence of perioperative non-fatal myocardial infarction in vascular surgery is 8.5% when the patients have proven coronary artery disease, but only 1.6% in patients with no risk factors, and 1.9% if the patient has had a CABG;[21 118] the latter results are obtained in patients who survived at least 6 months after their cardiac operation.

The data might seem to support prophylactic CABG. However, the mortality/morbidity of coronary revascularization, of a non-cardiac procedure and of postponement of vascular surgery must be added.[28 31] The mortality of vascular patients in cardiac surgery (6.5%) is much higher than the mortality of patients without vascular disease (0.5–2%).[8 31 50 82 98 99] Prior CABG offers no short-term benefit to these patients. In a decision analysis study comparing the strategy of prior coronary revascularization *vs* proceeding directly to vascular surgery, Mason and colleagues found poorer overall short-term outcomes with the combined procedures for the four end points of non-fatal myocardial infarction, stroke, cost, and mortality.[75] The indication for revascularization is the potential long-term benefit of an increased survival, independent of non-cardiac operative events. Routine coronary angiography in vascular patients does not provide short-term perioperative benefit.[44]

In a retrospective study on 6895 US Medicare patients, it appears that coronary revascularization has a protective effect on cases undergoing abdominal aortic surgery (fall in mortality from 4.1 to 2.8%), but not on those who underwent infra-inguinal vascular surgery.[35] In older patients (>70 yr), the benefit of previous coronary revascularization is probably non-existent, as mortality correlated to CABG or PTCA increases with age and the potential life-prolonging effect decreases. Finally, the benefit from CABG or PTCA may vary considerably between different institutions or different surgeons: when the perioperative mortality of abdominal aortic surgery is low (<3%), preoperative testing for coronary artery disease becomes insignificant in modifying the clinical outcome, and previous revascularization is no longer necessary in all but highly symptomatic patients.[106]

Pharmacological pretreatment

Is any pharmacological perioperative treatment protective against ischaemia? In the past, controlled studies with nitrates, calcium-channel blockers, clonidine, or digoxin have all produced negative answers.[7 13 18 25 94] More recent prospective randomized studies have focused on the use of beta-blockers with favourable results.[127] In both vascular and general surgery, the cardiac perioperative mortality is reduced by 8% and the ischaemic complication rate by 15% in patients treated with atenolol.[71] Among vascular patients with abnormal DSE, cardiac mortality, and morbidity are lowered from 34% in a control group to 3.4% in a group treated with bisoprolol.[90] Perioperative beta-block reduces the mortality of vascular patients in all risk categories except in patients with unstable coronary syndromes needing revascularization, as indicated by extensive ischaemia induced at DSE.[11] The treatment is started a few days before surgery, and continued during the first postoperative week. The dose is titrated to achieve a resting heart rate between 50 and 60 beats min^{-1}.[22] Older age is not a contraindication.[126] If preoperative administration is not possible, i.v. beta-block at the start of anaesthesia, followed by continuous postoperative treatment, is also efficient.[120] During a 3-yr follow-up, continuous administration of bisoprolol also protects from late ischaemic cardiac events after vascular surgery.[89 91] As sympathetic stimulation and tachycardia are among the most important factors in the development of perioperative myocardial ischaemia, and as ischaemia might appear in an insignificantly stenosed coronary artery, it is not surprising that sympathetic block is an effective method of preventing cardiac morbidity and mortality in non-cardiac surgery, as it is in non-surgical patients after myocardial infarction.[26 43 46 69] There might be non-responders, as recent investigations have disclosed less effect of beta-block in American black individuals than in the white population.[24 124]

As a consequence, in patients with known, or at risk of coronary artery disease, beta_1-selective antagonists should be considered in the perioperative period when these patients are to undergo major or vascular surgery. Despite the concern of many anaesthetists, the benefits of fewer cardiac complications in patients with coronary artery disease outweigh the risks of adverse effects in stage IV peripheral arterial disease, diabetes, and obstructive lung disease.[11 34 112 121 127] In most cases, the risk of non-cardiac surgery alone with prophylactic beta_1-block is lower than the cumulative risk of coronary angiography, a revascularization procedure and a non-cardiac vascular operation.[10 64]

Nevertheless, the recent trend towards beta_1-antagonism is essentially based on six publications summing up a total of 502 patients receiving perioperative beta-block.[11 71 90 91 120 126] Only three of them are randomized (total, 201 beta-block patients),[71 90 126] and only two are outcome studies (158 beta-block patients *vs* 154 controls, short- and long-term follow-up).[71 90 91 120] Obviously, more

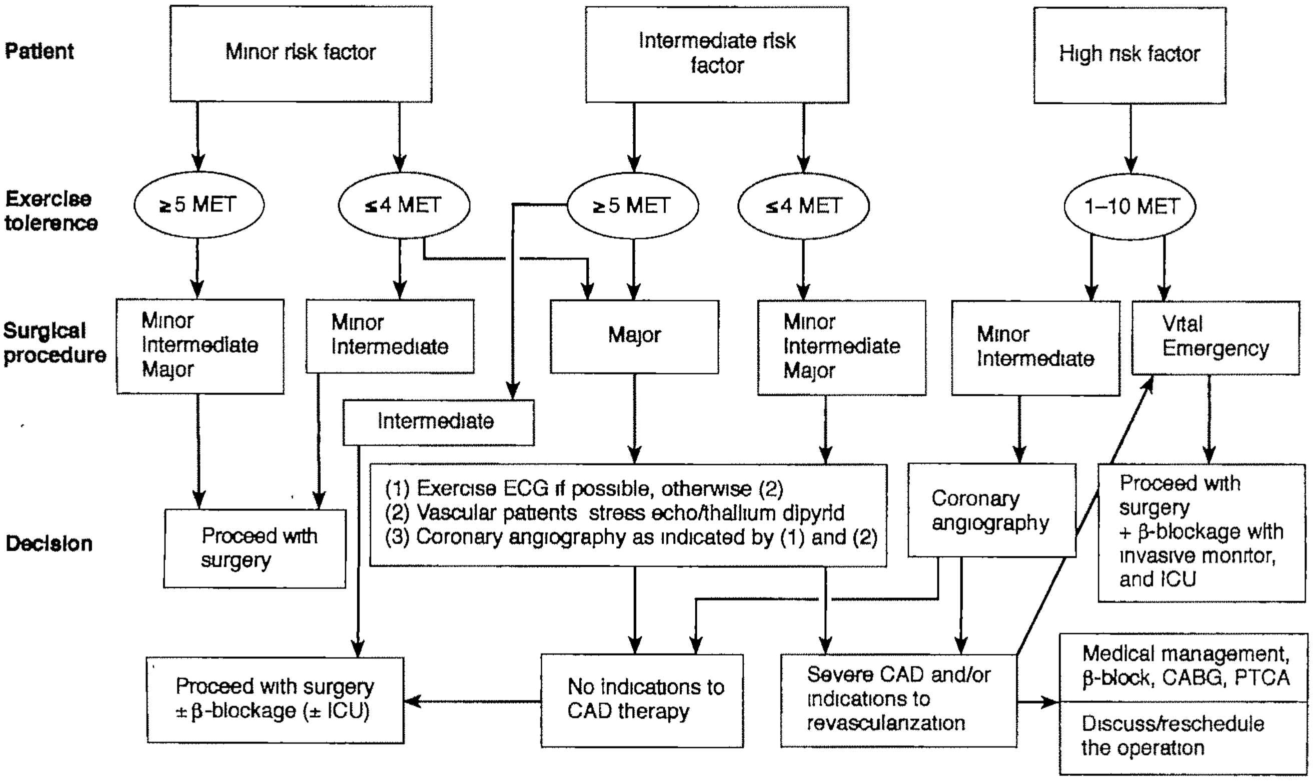


Fig 1 Algorithm for evaluating patients suffering from, or at risk of, myocardial ischaemia.

studies are needed before this therapy can be presented as state-of-the-art management.

Algorithm

The American College of Cardiology/American Heart Association Guidelines for Perioperative Cardiovascular Evaluation for Noncardiac Surgery have promoted recommendations based on evidence and expert opinions, and summarized them in a decisional algorithm which has proven efficient and cost-effective when tested on clinical patients for vascular surgery.[5,20,22] The American College of Physicians has adopted a position based on a meta-analysis of studies considered of strong, fair, or weak quality, and proposed an algorithm based on a modified cardiac risk index;[1,84] vascular and non-vascular surgery are separated. Other workers have published their own views on preoperative cardiac assessment, and have suggested useful paradigms.[36,56,72,74,115]

In our proposition (Fig. 1), the algorithm starts with a stratification of patients in three categories on the basis of clinical predictors (Table 1): low-risk (increased probability of coronary artery disease), intermediate-risk (stable coronary artery disease), and high-risk (unstable coronary syndrome). It proceeds through two evaluation steps: the exercise tolerance of the patient (cut-off point between 4 and 5 MET, Table 2) and the importance of the surgical procedure (minor, intermediate, or major, Table 3). Stress tests are performed only in the intermediate-risk category. Coronary angiography is considered in patients with unstable coronary syndromes or with stress tests revealing large areas of myocardium at risk. High-risk patients should undergo only mandatory or emergency procedures; anaesthesia should then be provided by an experienced anaesthetist using invasive monitoring and aggressive treatment of haemodynamic or ischaemic abnormalities. The choice of anaesthesia technique, like use of epidural analgesia, might be of significance in cardiac morbidity and mortality, but this is outside the scope of this review.[6,9]

Conclusions

Several studies have addressed the problem of preoperative evaluation of patients known to have, or at risk of, coronary artery disease. Nevertheless, in the absence of large, randomized, multicentre studies with clear-cut results, we have to rely on evidence-based medicine and Bayesian analysis for choosing preoperative strategies. The proposed framework suggests a rather conservative approach, limiting stress testing to intermediate-risk patients with suspicion of a myocardium at risk of ischaemia, and coronary angiography to situations where revascularization can improve long-term survival. A specialized and costly test is indicated only when the additional information provided has a positive impact on patient outcome.

Recent publications tend to show an increased risk of proceeding with non-cardiac surgery less than 3 months after coronary revascularization, which has been demonstrated to have no place in preventing the ischaemic complications of non-cardiac operations. Moreover, it is frequently impossible to wait to treat myocardial ischaemia when the patient requires a life-saving operation. In these situations, recent studies, although scarce, have demonstrated a marked benefit of operating under the protection of beta$_1$-adrenergic antagonism. As postoperative infarction has a better correlation with peri- and postoperative ischaemic events than with preoperative ischaemia, it seems logical to be aggressive in the prevention and treatment of perioperative events. Finally, it appears that the best strategy is very institution-specific. Every institution should construct its own guidelines, based on local performances and results.

To help clarifying the comparison between different publications with dissimilar methodologies, the references are annotated into levels of evidence according to the guidelines of evidence-based medicine. Level I of evidence contains large studies with prospective, randomized selection of patients, blinding, and clear-cut results. Level II contains small, randomized trials with uncertain results. Level III comprises non-randomized studies with contemporaneous controls. Level IV corresponds to non-randomized studies with historical controls. Level V includes uncontrolled case series and expert opinions. Theoretical models, meta-analyses, and guidelines are not coded.

References

1 ACP—American College of Physicians. Guidelines for assessing and managing the perioperative risk from coronary artery disease associated with major noncardiac surgery *Ann Intern Med* 1997, **127**: 309–12

2 ADA—American Diabetes Association. Consensus development conference on the diagnosis of coronary heart disease in people with diabetes. *Diabetes Care* 1998; **21**: 1551–9

3 Ashton CM, Petersen NJ, Wray NP, *et al.* The incidence of perioperative myocardial infarction in men undergoing noncardiac surgery. *Ann Intern Med* 1993, **118**: 504–10 (Level III)

4 Baron JF, Mundler O, Bertrand M, *et al.* Dipyridamole-thallium scintigraphy and gated radionuclide angiography to assess cardiac risk before abdominal aortic surgery. *N Engl J Med* 1994; **330**: 663–9 (Level III)

5 Bartels C, Bechtel M, Hossmann V, Horsch S. Cardiac risk stratification for high-risk vascular surgery. *Circulation* 1997; **95**: 2473–5 (Level II)

6 Beattie Ws, Badner NH, Choi P. Epidural analgesia reduces postoperative myocardial infarction: a meta-analysis. *Anesth Analg* 2001; **93**: 853–8

7 Bille-Brahé E, Engell HC, Bredgaard-Sorensen M. Acute postoperative digitalization of patients with arteriosclerotic heart disease after major surgery: randomized hemodynamic study and proposal for therapy. *Acta Anaesthesiol Scand* 1980; **24**: 501–6 (Level II)

8 Birkmeyer JD, O'Connor FT, Quinton HB, *et al.* The effect of peripheral vascular disease on in-hospital mortality rates with coronary bypass surgery. *J Vasc Surg* 1995; **21**: 445–52 (Level III)

9 Bode RH, Lewis KP, Zarich SW, *et al.* Cardiac outcome after peripheral vascular surgery. Comparison of general and regional anesthesia. *Anesthesiology* 1996; **84**. 3–13 (Level II)

10 Bodenmeier MM. Noncardiac surgery in the cardiac patient: what is the question? *Ann Intern Med* 1996; **124**: 763–6 (Level V)

11 Boersma E, Poldermans D, Bax JJ, *et al.* Predictors of cardiac events after major vascular surgery. Role of clinical characteristics, dobutamine echocardiography, and β-blocker therapy. *JAMA* 2001; **285**. 1865–73 (Level II)

12 Brown KA, Rowen M. Extent of jeopardized viable myocardium determined by myocardial perfusion imaging best predicts perioperative cardiac events in patients undergoing noncardiac surgery. *J Am Coll Cardiol* 1993, **21**: 325–30 (Level III)

13 Chung F, Houston PL, Cheng DC, *et al.* Calcium channel blockade does not offer adequate protection from perioperative myocardial ischemia. *Anesthesiology* 1988; **69**: 343–7 (Level II)

14 Cohen MC, Curran PJ, L'Italien GJ, Mittelman MA, Zarich SW. Long-term prognostic value of preoperative dipyridamole-thallium imaging and clinical indexes in patients with diabetes mellitus undergoing peripheral vascular surgery. *Am J Cardiol* 1999; **83**. 1038–42 (Level III)

15 Cutlip DE, Baim DS, Ho KKL, *et al.* Stent thrombosis in the modern era. A pooled analysis of multicenter coronary stent clinical trial. *Circulation* 2001; **103**: 1967–71 (Level III)

16 Desprez RD, Friesinger GC, Red GW, *et al.* A simple accurate model for predicting myocardial infarction after general surgery (abstract). *Circulation* 1995; **92**: S744(Level III)

17 Detre K, Yeh W, Kesley S, *et al.* Has improvement in PTCA intervention affected long-term prognosis? The NHLBI PTCA Registry experience *Circulation* 1995; **91**: 2868–75 (Level III)

18 Dodds TM, Stone JG, Coromilas J, Weinberger M, Levy DG. Prophylactic nitroglycerine infusion during noncardiac surgery does not reduce perioperative ischemia. *Anesth Analg* 1993, **76**: 705–13 (Level II)

19 Eagle KA, Coley CM. Newell JB, *et al.* Combining clinical and thallium data optimizes preoperative assessment of cardiac risk before vascular surgery. *Ann Intern Med* 1989; **110**: 859–66 (Level III)

20 Eagle KA, Brundage BH, Chaitman BR, *et al.* Guidelines for perioperative cardiovascular evaluation for non-cardiac surgery. Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 1996; **93**: 1278–317

21 Eagle KA, Rihal CS, Mickel MC, Holmes DR, Foster ED, Gersh BJ. Cardiac risk of non-cardiac surgery: influence of coronary disease and type of surgery in 3,368 operations. *Circulation* 1997; **96**: 1882–7 (Level III)

22 Eagle KA, Berger PB, Calkins H, *et al.* ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery—executive summary. A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee to update 1996 guidelines on perioperative cardiovascular evaluation for noncardiac surgery). *Circulation* 2002; **105**: 1257–67

23 Eichelberger JP, Schwarz KQ, Black ER, Green RM, Ouriel K. Predictive value of dobutamine echocardiography just before noncardiac vascular surgery. *Am J Cardiol* 1993; **72**: 602–7 (Level III)

24 Eichhorn E, Domanski M, Krause-Steinrauf H, *et al.* The Beta-blocker Evaluation of Survival Trial (BEST). A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. *N Engl J Med* 2001; **344**: 1659–67 (Level I)

25 Ellis JE, Pedlow S, Laff SP, *et al* Premedication with oral and transdermal clonidine provides safe and efficacious postoperative sympatholysis. *Anesth Analg* 1994; **79**: 1133–40 (Level III)

26 Ellis SG, Hertzer NR, Young JR, Brener S. Angiographic correlates of cardiac death and myocardial infarction complicating major non-thoracic vascular surgery. *Am J Cardiol* 1996, **77**: 1126–8 (Level III)

27 Elmore JR, Hallett JW, Gibbons RJ, *et al* Myocardial revascularization before abdominal aortic aneurysmorrhaphy effect of coronary angioplasty. *Mayo Clin Proc* 1993; **68**: 637–41 (Level III)

28 Fehr DM, Chambers CE, Thiele B, Mangano D, Kingsley CP. Case 4–1995 Perioperative myocardial infarction in a patient undergoing abdominal aortic aneuvrysm resection: perioperative risk assessment *J Cardiothorac Vasc Anesth* 1995; **9**: 452–9 (Level V)

29 Ferrara N, Longobardi G, Nicolino A, *et al*. Effect of beta-adrenoreceptor blockade on dipyridamole-induced myocardial asynergies in coronary artery disease *Am J Cardiol* 1992; **70**. 724–7 (Level I)

30 Fleisher LA, Rosenbaum SH, Nelson AH, Barash PG. The predictive value of preoperative silent ischemia for postoperative ischemic cardiac events in vascular and nonvascular surgery patients. *Am Heart J* 1991; **122**: 980–6 (Level II)

31 Fleisher LA, Skolnick ED, Holroyd KJ, Lehman HP. Coronary artery revascularization before abdominal aortic aneurysm surgery: a decision analytic approach. *Anesth Analg* 1994; **79**. 661–9

32 Fleisher LA, Rosenbaum SH, Nelson AH, Jain D, Wackers FJ, Zaret BL Preoperative dipyridamole-thallium imaging and ambulatory electrocardiographic monitoring as a predictor of perioperative cardiac events and long-term outcome. *Anesthesiology* 1995; **83**: 906–17 (Level III)

33 Fleisher LA, Eagle KA. Screening for cardiac disease in patients having noncardiac surgery. *Ann Intern Med* 1996; **124**: 762–72 (Level V)

34 Fleisher LA Con: β-blockers should not be used in all patients undergoing vascular surgery. *J Cardiothorac Vasc Anesth* 1999; **13**: 496–7 (Level V)

35 Fleisher LA, Eagle KA, Schaffer T, Anderson GF. Perioperative and long-term mortality rates after major vascular surgery: The relationship to preoperative testing in the Medicare population. *Anesth Analg* 1999, **89**· 849–55 (Level III)

36 Fleisher LA, Eagle KA. Lowering cardiac risk in noncardiac surgery. *N Engl J Med* 2001; **345**: 1677–82 (Level V)

37 Foster ED, Davis KB, Carpentier JA, Abele S, Fray D. Risk of noncardiac operation in patients with defined coronary disease: The Coronary Artery Surgery Study (CASS) registry experience *Ann Thorac Surg* 1986; **41**: 42–50 (Level III)

38 Frye RL, Alderman E, Bourassa M, Brouks MM, Califf R, Chaitman B. Influence of diabetes on 5-year mortality and morbidity in a randomized trial comparing CABG and PTCA in patients with multivessel disease. the Bypass Angioplasty Revascularization Investigation (BARI). *Circulation* 1997; **96**: 1761–9 (Level I)

39 Gauss A, Rohm HJ, Schauffelen A, *et al*. Electro-cardiographic exercise stress testing for cardiac risk assessment in patients undergoing noncardiac surgery. *Anesthesiology* 2001; **94**: 38–46 (Level II)

40 Gersh BJ, Rihal CS, Rooke TW, Ballard DJ. Evaluation and management of patients with peripheral vascular and coronary disease. *J Am Coll Cardiol* 1991, **18**: 203–14 (Level V)

41 Gianrossi R, Detrano R, Mulvihill D, *et al*. Exercise-induced ST-depression in the diagnosis of coronary artery disease A meta-analysis. *Circulation* 1989, **80**. 87–98

42 Girish M, Trayner E, Dammann O, Pinto-Plata V, Celli B. Symptom-limited stair climbing as a predictor of postoperative cardiopulmonary complications after high-risk surgery. *Chest* 2001; **120**: 1147–51 (Level III)

43 Giroud D, Li JM, Urban P, Meier B, Rutishauser W. Relation of the site of acute myocardial infarction to the most severe coronary arterial stenosis at prior angiography. *Am J Cardiol* 1992; **69**: 729–32 (Level III)

44 Glance LG. Selective preoperative cardiac screening improves five-year survival in patients undergoing major vascular surgery: a cost-effectiveness analysis *J Cardiothor Vasc Anesth* 1999, **13**· 265–71

45 Gottlieb A, Banoub M, Sprung J, Levy PV, Beven M, Masha EJ. Perioperative cardiovascular morbidity in patients with coronary artery disease undergoing vascular surgery after percutaneous transluminal coronary angioplasty. *J Cardiothor Vasc Anesth* 1998; **12**: 501–6 (Level III)

46 Gottlieb SS, McCarter RJ, Vogel RA Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction *N Engl J Med* 1998; **339**: 489–97 (Level III)

47 Grundy SM, Benjamin IJ, Burke GL, *et al*. Diabetes and cardiovascular disease. A statement for healthcare professionals from the American Heart Association. *Circulation* 1999; **100**· 1134–46 (Level V)

48 Haffner SM, Lehto S, Rennemaa T, Pyorala, Laakso M Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998, **339**. 229–34 (Level III)

49 Halm EA, Browner WS, Tubau JF, Tateo IM, Mangano DT Echocardiogaphy for assessing cardiac risk in patients having noncardiac surgery. *Ann Intern Med* 1996; **125**: 433–41 (Level III)

50 Hartz AJ, Kuhn EM, Pryor DB, Krakauer H, Young M, Heudebert G, Rimm AA. Mortality after coronary angioplasty and coronary artery bypass surgery (the National Medicare experience). *Am J Cardiol* 1992; **70**: 179–85 (Level III)

51 Hassan SA, Hlatky MA, Boothroyd DB, *et al*. Outcomes of noncardiac surgery after coronary bypass surgery or coronary angioplasty in the Bypass Angioplasty Revascularization Investigation (BARI). *Am J Med* 2001; **110**· 260–6 (Level I)

52 Hertzer NR, Beven EG, Young JR, *et al* Coronary artery disease in peripheral vascular patients: a classification of 1000 coronary angiograms and results of surgical management. *Ann Surg* 1984; **199**: 223–33 (Level IV)

53 Hertzer NR. Basic data concerning coronary disease in peripheral vascular patients. *Ann Vasc Surg* 1987, **1**. 616–20 (Level IV)

54 Hlatky P, Boineau RE, Higginbotham MB, *et al* A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). *Am J Cardiol* 1989; **64** 651–4 (Level V)

55 Hohner P, Nancarrow C, Backman C, *et al*. Anesthesia for abdominal vascular surgery in patients with coronary artery disease. Part I· isoflurane produces dose-dependent coronary vasodilatation. *Acta Anaesthesiol Scand* 1994; **38**· 780–92 (Level II)

56 Hollenberg SM. Preoperative cardiac risk assessment *Chest* 1999; **115**: 51S–7S

57 Howell SJ, Sear YM, Yeates D, Goldacre M, Sear JW, Foex P Risk factors for cardiovascular death after elective surgery under general anaesthesia. *Br J Anaesth* 1998; **80**. 14–9 (Level IV)

58 Huber KC, Evans MA, Bresnahan JF, Gibbons RJ, Holmes DR. Outcome of noncardiac operations in patients with severe coronary artery disease successfully treated preoperatively with coronary angioplasty. *Mayo Clin Proc* 1992; **67**: 15–21 (Level III)

59 Kaaja R, Sell H, Erkola O, Harjula A. Predictive value of manual ECG-monitored exercise test before abdominal aortic or peripheral vascular surgery. *Angiology* 1993; **44**: 11–5 (Level II)

60 Kaluza GL, Joseph J, Lee RJ, Raizner ME, Raizner AE. Catastrophic outcomes of noncardiac surgery soon after coronary stenting. *J Am Coll Cardiol* 2000; **35**: 1288–94 (Level IV)

61 Khuri SF, Daley J, Henderson W, *et al.* The National Veterans Administration Surgical Risk Study: risk adjustment for the comparative assessment of the quality of surgical care. *J Am Coll Surg* 1995; **180**: 519–31 (Level III)

62 Landesberg G, Einav S, Christopherson R, *et al.* Perioperative ischemia and cardiac complications in major vascular surgery: importance of the preoperative twelve-lead electrocardiogram. *J Vasc Surg* 1997; **26**: 570–8 (Level III)

63 Lane RT, Sawada SG, Segar DS, *et al.* Dobutamine stress echocardiography for assessment of cardiac risk before noncardiac surgery. *Am J Cardiol* 1991; **68**. 976–7 (Level IV)

64 Lee TH. Reducing cardiac risk in noncadiac surgery. *N Engl J Med* 1999; **341**: 1838–40 (Level V)

65 Lee TH, Marcantonio ER, Mangione CM, *et al.* Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation* 1999; **100**: 1043–9 (Level I)

66 L'Italien GJ, Paul SD, Hendel RC, *et al.* Development and validation of a Bayesian model for perioperative cardiac risk assessment in a cohort of 1,081 vascular surgical candidates. *J Am Coll Cardiol* 1996; **27**: 779–86 (Level III)

67 Mangano DT, Browner WS, Hollenberg M, London MJ, Tubau JF, Tateo IM. Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. The Study of Perioperative Ischemia Research Group. *N Engl J Med* 1990; **323**: 1781–8 (Level III)

68 Mangano DT, London MJ, Tubau JF, *et al* Dipyridamole-thallium-201 scintigraphy as a preoperative screening test. A reexamination of its predictive potential. *Circulation* 1991; **84**: 493–502 (Level III)

69 Mangano DT, Wong MG, London MJ, Tubau JF, Rapp JA. Perioperative myocardial ischemia in patients undergoing noncardiac surgery—II: Incidence and severity during the 1st week after surgery. The Study of Perioperative Ischemia Research Group. *J Am Coll Cardiol* 1991; **17**: 851–7 (Level III)

70 Mangano DT, Goldman L. Preoperative assessment of patients with known or suspected coronary disease. *N Engl J Med* 1995; **333**: 1750–6 (Level V)

71 Mangano DT, Layug EL, Wallace A, Tateo IM. Effects of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. The multicenter study of Perioperative Ischemia Research Group. *N Engl J Med* 1996; **335**: 1713–20 (Level II)

72 Mangano DT. Assessment of the patient with cardiac disease. An anesthesiologist's paradigm. *Anesthesiology* 1999; **91**: 1521–6 (Level V)

73 Mantha S, Roizen MF, Barnard J, Thisted RA, Ellis JE, Foss J. Relative effectiveness of four preoperative tests for predictive adverse cardiac outcome after vascular surgery. *Anesth Analg* 1994; **79**: 422–33

74 Mantha S. Rational cardiac risk stratification before peripheral vascular surgery. application of evidence-based medicine and Bayesian analysis. *Semin Cardiothorac Vasc Anesth* 2000, **4**: 198–212 (Level V)

75 Mason JJ, Owens DK, Harris RA, Cooke JP, Hlatky MA. The role of coronary angiography and coronary revascularization before noncardiac surgery *JAMA* 1995, **273**: 1919–25

76 Mathes DD. The preoperative evaluation of the patient with cardiac risk factors for noncardiac surgery: which patients need further cardiac risk stratification tests? *Semin Cardiothorac Vasc Anesth* 2001; **5**: 154–65 (Level V)

77 McCann RL Wolfe WG. Resection of abdominal aortic aneuvrysm in patients with low ejection fraction. *J Vasc Surg* 1989; **10**: 240–4 (Level V)

78 McPhail N, Calvin JE, Shariatmadar A, Barber GG, Scobie TK. The use of preoperative exercise testing to predict cardiac complications after arterial reconstruction. *J Vasc Surg* 1988; **7**: 60–8 (Level III)

79 Metzler H. Preoperative interventional cardiology in noncardiac surgery: benefit or risk? *Curr Opin Anaesthesiol* 2001; **14**: 1–2 (Level V)

80 Mizuno K, Miyamoto A, Satomura K, *et al.* Angioscopic coronary macromorphology in patients with acute coronary disorders *Lancet* 1991; **337**. 809–12 (Level III)

81 Morris CK, Ueshima K, Kawaguchi T, Hideg A, Froelicher VF. The prognostic value of exercise capacity: a review of the literature. *Am Heart J* 1991; **122**. 1423–31

82 Olsen PS, Schroeder T, Agerskov K, *et al.* Surgery for abdominal aortic aneuvrysms. A survey of 656 patients. *J Cardiovasc Surg* 1991; **32**: 636–42 (Level IV)

83 Ouriel K, Green RM, Deweese JA, Varon ME. Outpatient echocardiography as a predictor of perioperative cardiac morbidity after peripheral vascular surgical procedures. *J Vasc Surg* 1995; **22**: 671–9 (Level IV)

84 Palda VA, Detsky AS. Perioperative assessment and management of risk from coronary artery disease *Ann Intern Med* 1997; **127**: 313–28

85 Paul SD, L'Italien GJ, Hendel RC, Leppo JA, Eagle KA. Influence of prior heart disease on morbidity and mortality after vascular surgery: role of coronary artery bypass grafting (abstract). *J Am Coll Cardiol* 1994; **24**: 952–133, 380A (Level III)

86 Paul SD, Eagle KA, Kuntz KM, Young JR, Hertzer NR. Concordance of preoperative clinical risk with angiographic severity of coronary artery disease in patients undergoing vascular surgery. *Circulation* 1996; **94**: 1561–6 (Level III)

87 Poldermans D, Fioretti PM, Forster T, *et al.* Dobutamine stress echocardiography for assessment of perioperative cardiac risk in patients undergoing major vascular surgery. *Circulation* 1993; **87**: 1506–12 (Level III)

88 Poldermans D, Arnese M, Fioretti P, *et al.* Improved cardiac risk stratification in major vascular surgery with dobutamine-atropine stress echocardiography. *J Am Coll Cardiol* 1995; **26**. 648–53 (Level III)

89 Poldermans D, Arnese M, Fioretti PM, et *al.* Sustained prognostic value of dobutamine stress echocardiography for late cardiac events after major noncardiac vascular surgery. *Circulation* 1997, **95**: 53–8 (Level III)

90 Poldermans D, Boersma E, Bax JJ, *et al.* The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. *N Engl J Med* 1999; **341**: 1789–94 (Level II)

91 Poldermans D, Boersma E, Bax JJ, *et al.* Bisoprolol reduces cardiac death and myocardial infarction in high-risk patients as long as 2 years after successful major vascular surgery. *Eur Heart J* 2001; **22**: 1353–8 (Level II)

92 Posner KL, van Norman GA, Chan V. Adverse cardiac outcome after noncardiac surgery in patients with prior percutaneous transluminal coronary angioplasty. *Anesth Analg* 1999; **89**: 553–60 (Level IV)

93 Priebe HJ. The aged cardiovascular risk patient. *Br J Anaesth* 2000; **85**. 763–78 (Level V)

94 Quentin L, Bouilloc X, Butin E, *et al.* Clonidine for major vascular surgery in hypertensive patients: a double-blind, controlled, randomized trial. *Anesth Analg* 1996; **83**: 687–95 (Level I)

95 Raby KE, Goldman L, Creager MA, *et al.* Correlation between preoperative ischemia and major cardiac events after peripheral vascular surgery. *N Engl J Med* 1989; **321**: 1296–300 (Level III)

96 Raby KE, Barry J, Creager MA, Cook EF, Weisberg MC, Goldman L. Detection and significance of intraoperative and postoperative myocardial ischemia in peripheral vascular surgery. *JAMA* 1992; **268**: 222–7 (Level III)

97 Rao TL, Jacobs KH, El-Etr AA. Reinfarction following anesthesia in patients with myocardial infarction. *Anesthesiology* 1983; **59**: 499–505 (Level IV)

98 Rihal CS, Eagle KA, Mickel MC, Foster ED, Sopko G, Gersh BJ. Surgical therapy for coronary artery disease among patients with combined coronary artery and peripheral vascular disease. *Circulation* 1995; **91**: 46–53 (Level IV)

99 Rihal CS, Sutton-Tyrell K, Schaff HV, *et al.* Increased incidence of complications among patients with peripheral vascular disease following coronary bypass grafting and angioplasty. *Circulation* 1997; **96**: 467–8 (Level III)

100 Robotham JL, Takata M, Berman M. Ejection fraction revisited. *Anesthesiology* 1991; **74**: 172–83

101 Roizen MF. Are you as young as you could be? *Anesth Analg* 2000; **70**: 58–64 (Suppl) (Level V)

102 Rossi E, Citterio F, Vescio MF, *et al.* Risk stratification of patients undergoing peripheral vascular revascularization by combined resting and dipyridamole echocardiography. *Am J Cardiol* 1998; **82**: 306–10 (Level III)

103 Ruiz J, Keller U, Buillard C. Prévention et dépistage de la maladie coronarienne chez le patient diabétique. *Bull Méd Suisses* 2000; **81**: 2596–600

104 Ryan TJ, Bauman WB, Kennedy JW, *et al.* ACC/AHA Task Force report: guidelines for percutaneous transluminal coronary angioplasty. A report of the ACC/AHA Task Force on assessment of diagnostic and therapeutic cardiovascular procedures. *J Am Coll Cardiol* 1993; **22**: 2033–54

105 Ryan TJ, Antman EM, Brooks NH. 1999 update: ACC/AHA guidelines for the management of patients with acute myocardial infarction: executive summary and recommendations. *Circulation* 1999; **100**: 1016–30

106 Seeger JM, Rosenthal GR, Self SB, Flynn TC, Limacher MC, Harward TRS. Does routine stress-thallium cardiac scanning reduce postoperative cardiac complications? *Ann Surg* 1994; **219**: 654–63 (Level III)

107 Sessler DI. Complications and treatment of mild hypothermia. *Anesthesiology* 2001; **95**: 531–43 (Level V)

108 Shaw LJ, Eagle KA, Gersh BJ, Miller DD. Meta-analysis of intravenous dipyridamole-thallium-201 imaging (1985–1994) and dobutamine stress echocardiography (1991–1994) for risk stratification before vascular surgery. *J Am Coll Cardiol* 1996; **27**: 787–98

109 Steen PA, Tinker JH, Tarhan S. Myocardial reinfarction after anaesthesia and surgery. *JAMA* 1978; **239**: 2566–70 (Level IV)

110 Steinberg JB, Kresowik TF, Behrendt DM. Prophylactic myocardial revascularization based on dipyridamole-thallium scanning before vascular surgery. *Cardiovasc Surg* 1993; **1**: 552–7 (Level IV)

111 Suggs WD, Smith RB, Weintraub WS, Dodson TF, Salam AA. Selective screening for coronary artery disease in patients undergoing elective repair of abdominal aortic aneuvrysm. *J Vasc Surg* 1993; **18**: 349–57 (Level III)

112 Sutton T, Rock P. Pro: β-blockers should be used in all patients undergoing vascular surgery. *J Cardiothorac Vasc Anesth* 1999; **13**. 490–5 (Level V)

113 Takase B, Younis LT, Byers SL, *et al.* Comparative prognostic value of clinical risk indexes, resting two-dimensional echocardiography, and dipyridamole stress thallium-201 myocardial imaging for perioperative cardiac events in major nonvascular surgery patients. *Am Heart J* 1993; **126**: 1099–106 (Level III)

114 Tarhan S, Moffitt SA, Taylor WF. Myocardial infarction after general anesthesia. *JAMA* 1972; **220**: 1451–4 (Level IV)

115 Tuman KJ. Perioperative cardiovascular risk: assessment and management. *Anesth Analg* 2001; **92**: S106–12 (Level V)

116 VanBelle E, Lablanche JM, Bauters C Coronary angioscopic findings in the infarcted-related vessel within 1 month of acute myocardial infarction. Natural history and the effect of thrombolysis. *Circulation* 1998; **97**: 26–33 (Level IV)

117 VanRoyen N, Jaffe CC, Krumholz HM, *et al.* Comparison and reproductibility of visual echocardiographic and quantitative radionuclide left ventricular ejection fractions. *Am J Cardiol* 1996; **77**: 843–50 (Level II)

118 Vanzetto G, Machecourt J, Blendea D, *et al.* Additive value of thallium single-photon emission computed tomography myocardial imaging for prediction of perioperative events in clinically selected high cardiac risk patients having abdominal aortic surgery. *Am J Cardiol* 1996; **77**: 143–8 (Level III)

119 Vicenzi MN, Ribitsch E, Luha O, Klein W, Metzler H. Coronary artery stenting before noncardiac surgery: more threat than safety? *Anesthesiology* 2001; **94**: 367–8 (Level V)

120 Wallace A, Layug B, Tateo I, *et al.* Prophylactic atenolol reduces postoperative myocardial ischemia. *Anesthesiology* 1998; **88**: 7–17 (Level II)

121 Warltier DC. β-Adrenergic blocking drugs. Incredibly useful, incredibly underutilized. *Anesthesiology* 1998; **88**. 2–5 (Level V)

122 Weiner D, Ryan TJ, McCabe CH, Chaitman BR, Sheffield LT, Fisher LD. Prognostic importance of a clinical profile and exercise test in medically treated patients with coronary artery disease. *J Am Coll Cardiol* 1984; **3**: 772–9 (Level III)

123 Weissman NJ, Levangie MW, Guerrero JL, Weyman AE, Picard MH. Effect of β-blockade on dobutamine stress echocardiography. *Am Heart J* 1996, **131**: 698–703 (Level II)

124 Yancy CW, Fowler MB, Colucci WS, *et al.* Race and the response to adrenergic blockade with carvedilol in patients with chronic heart failure. *N Engl J Med* 2001; **344**: 1358–65 (Level II)

125 Younis L, Stratmann H, Takase B, Byers S, Chaitman BR, Miller DD. Perioperative clinical assessment and dipyridamole thallium-201 scintigraphy for prediction and prevention of cardiac events in patients having noncardiovascular surgery and known or suspected coronary artery disease. *Am J Cardiol* 1994; **74**: 311–7 (Level III)

126 Zaugg M, Tagliente T, Luchinetti E, *et al.* Beneficial effects of β-adrenergic blockade in elderly patients undergoing noncardiac surgery. *Anesthesiology* 1999; **91**: 1674–86 (Level II)

127 Zaugg M, Schaub MC, Pasch T, Spahn DR. Modulation of β-adrenergic receptor subtype activities in perioperative medecine: Mechanisms and sites of action. *Br J Anaesth* 2002; **88**: 101–23

British Journal of Anaesthesia 89 (5): 760–1 (2002)

SHORT COMMUNICATIONS

Patient preferences for immediate postoperative recovery

L. H. J. Eberhart*, **A. M. Morin**, **H. Wulf** and **G. Geldner**

Department of Anaesthesiology and Intensive Care Medicine, Philipps-University of Marburg, Baldingerstrasse, D-35033 Marburg, Germany

**Corresponding author*

Background. Several attempts have been made to evaluate patients' concerns with respect to postoperative recovery. To identify aspects of postoperative recovery relevant to patients, several methodological and statistical approaches have been used. One of the first to provide useful information was Fredrick Orkin who used conjoint analysis. This methodology is usually performed by market researchers to learn about the relative importance of product attributes. We used conjoint analysis in the present study.

Methods. A total of 220 patients undergoing preoperative anaesthetic examination before impending surgery under general anaesthesia were asked to rate nine scenarios during immediate postoperative recovery based on four factors (alertness, pain, postoperative nausea and vomiting (PONV), and extra costs) each with three levels. Using conjoint analysis the relative impact of each factor on ranking the scenarios was assessed.

Results. The relative importance of the four factors (as a percentage of the preference decision) was PONV (49%), pain (27%), alertness (13%), and additional costs (11%).

Conclusion. Avoidance of PONV is a major concern for patients before surgery.

Br J Anaesth 2002; **89**: 760–1

Keywords: recovery, postoperative; vomiting, nausea

Accepted for publication: May 24, 2002

Improved surgical and anaesthetic techniques have minimized morbidity and mortality associated with surgery. In turn, anaesthetists have focused on other issues of importance to the patients. Several attempts have been made to evaluate the patients' concerns with respect to postoperative recovery. In these studies, different methodologies have been used, including traditional face to face or paper-based interviews,[1] willingness to pay,[2] or rating of virtual scenarios.[3]

One of the first to provide useful information about patients' preferences for their postoperative recovery was Fredrick Orkin who reported results from a survey of nurses, anaesthetists, support staff, and computer personnel at a national meeting.[4] Forty-seven subjects were asked to rate 16 scenarios of immediate postoperative recovery and 15 min were given to perform the rating. Conjoint analysis was used to judge the relative contribution of each item on the final scenario rating. It was found that postoperative nausea and vomiting (PONV) was a major concern. To prevent this complication, they were willing to accept other side-effects, including extra payment (15–50 US$). Although the interesting data have not yet been published as a full paper, numerous authors have quoted the abstract to confirm the importance of antiemetic strategies.

Thus, we felt that it would be interesting to apply Orkin's approach and evaluate whether the data can be reproduced in patients about to undergo surgery. The complex methodology used by Orkin[4] (six factors, up to four levels, resulting in a model with 16 scenarios and four additional scenarios for validation of computed utilities) was modified to allow a simple questionnaire with fewer scenarios.

Methods and results

A total of 250 consecutive patients (56% females; median age 48 (range 16–76) yr) undergoing orthopaedic (48%), gynaecological (28%), urological (10%),

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Table 1 The nine scenarios determined by an orthogonal main-effects plan for conjoint analysis

Scenario	Alertness	Pain	PONV	Extra costs
1	Exhausted	No	Nauseated	50 Euros
2	Clear minded	Moderate	Vomiting	50 Euros
3	Tired	No	Vomiting	25 Euros
4	Clear minded	No	No	0 Euros
5	Tired	Moderate	Nauseated	0 Euros
6	Clear minded	Mild	Nauseated	25 Euros
7	Exhausted	Mild	Vomiting	0 Euros
8	Tired	Mild	No	50 Euros
9	Exhausted	Moderate	No	25 Euros

or minor general surgical procedures (14%) performed under general anaesthesia were enrolled. Patients were interviewed after completing a preoperative visit. General information about the course and side-effects of anaesthesia was given. Of 250 patients, 28 were not able to understand the purpose of the studies. In two patients, only incomplete data was obtained. Thus, data of the remaining 220 patients was analysed. The Statistical Package for Social Sciences (SPSS, Version 10.1 for Windows) was used to create and analyse an orthogonal main-effects plan for the following four factors, each with three levels: (1) postoperative alertness, exhausted–tired–alert; (2) pain, moderate–mild or none; (3) nausea and vomiting, vomiting, nauseated or none; (4) additional costs, 50-25 Euros or none.

Conjoint analysis enables the measurement of consumer preferences or ratings of existing or possible products in terms of product attributes and their levels. The purpose of conducting a conjoint experiment is to ascertain the relative importance of product attributes, as well as the most preferred attribute levels.

Nine scenarios of postoperative recovery (out of 81 possible) (Table 1) were offered and the patients were asked to rate them from 1 (highly undesirable—would avoid this scenario if ever possible) to 9 (desirable—scenario of my choice for my impending operation) in a raising sequence. At this moment, patients knew that standardized anaesthesia care was offered and no extra money would be charged from them, regardless of their given answers.

Avoiding PONV was of major concern for the patients. This item was followed by the desire to have no or only mild pain. Restoration of postoperative vigilance and additional cost were of minor importance. The relative contributions (as percentages) of the different factors were: (1) (absence of) PONV, 49%; (2) (absence of) postoperative pain, 27%; (3) (absence of) postoperative sedation, 13%; (4) no extra charge, 11%.

Comment

Our results confirm those of Orkin. Avoidance of PONV and reducing postoperative pain should be a major goal in anaesthesia. However, there were some differences between the two surveys. For example we interviewed consecutive patients attending for surgery the next day, while Orkin surveyed medical staff and participants of a national meeting, probably most of them highly educated people. Thus, we used a simplified model, with a limited number of scenarios and less items and levels, in our trial to avoid exclusion of too many patients.

Macario[3] used a similar technique. Patients were asked to spend an amount of virtual money (100 US$) was prevent several unpleasant side-effects of anaesthesia.[3] Interestingly, the amount of money spent to prevent vomiting (18 US$) and nausea (12 US$) is greater than that to prevent other unpleasant side-effects, for example postoperative pain (17 US$) or shivering (8 US$). Concerns about PONV (23%) and postoperative pain (14%) were most often raised by patients when asked about preoperative fears before surgery.[1]

One limitation of the present study is that patients, due to instructions from our ethics committee, knew that a standardized anaesthesia technique was provided and that they were not actually charged regardless of their answers. However, dealing with virtual scenarios is a common situation when performing conjoint analysis and should not disprove our results. Furthermore, from other surveys using the willingness-to-pay method, we know that patients are not penny-pinching when their postoperative well-being is concerned. For example, patients are willing to pay 56–100 US$ for a totally effective antiemetic.[2]

It is concluded that, regardless of the surveying technique used,[1–4] avoidance of PONV followed by the control of postoperative pain are the key concerns for patients undergoing a surgical procedure under general anaesthesia. Patients are willing to accept other side-effects and also increased private costs, when PONV can be attenuated or even completely prevented.

References

1 van Wijk MG, Smalhout B. A postoperative analysis of the patients' view of anaesthesia in a Netherlands teaching hospital. *Anaesthesia* 1990, **45**: 679–82

2 Gan TJ, Sloan F, de L Dear G, El-Moalem HE, Lubarsky DA. How much are patients willing to pay to avoid postoperative nausea and vomiting? *Anesth Analg* 2001; **92**: 393–400

3 Macario A, Weinger M, Carney S, Kim A. Which clinical anesthesia outcomes are important to avoid? The perspective of patients. *Anesth Analg* 1999; **89**: 652–8

4 Orkin FK. What do patients want? Preferences for immediate postoperative recovery. *Anesth Analg* 1992; **74**: S225

British Journal of Anaesthesia 89 (5): 762–4 (2002)

Effect of diclofenac on cerebral blood flow velocity in patients with supratentorial tumours

S. J. Jones and J. Dinsmore*

Department of Anaesthesia, St George's Hospital, Blackshaw Road, London SW17 0NE, UK
**Corresponding author*

Background. The aim of this investigation was to determine the effects of diclofenac on cerebral blood flow. Middle cerebral artery blood flow velocity was measured in nine patients with supratentorial tumours.

Methods. Using a transcranial Doppler ultrasound, we measured the baseline mean and systolic cerebral blood flow velocity. Measurements were repeated following administration of diclofenac 75 mg i.v.

Results. There was no significant change in cerebral blood flow velocity. All other physiological variables remained constant.

Conclusion. Diclofenac does not cause a significant change in cerebral blood flow velocity in patients with supratentorial tumours.

Br J Anaesth 2002; **89**: 762–4

Keywords: analgesics, anti-inflammatory, non-steroidal, diclofenac; brain, cerebral blood flow; measurement techniques, transcranial Doppler

Accepted for publication: June 17, 2002

The non-steroidal anti-inflammatory drug (NSAID) diclofenac is used as a perioperative analgesic in our neurosurgical unit for awake craniotomy and supratentorial tumour resections. Indomethacin, another NSAID, is known to significantly decrease cerebral blood flow (CBF) and intracranial pressure without changing cerebral metabolic rate.[1] Animal studies using diclofenac show no change in CBF but this has not been studied in man.[2] Major changes in cerebral physiology with drugs such as indomethacin have significant clinical implications in neuroanaesthesia and it is important that the cerebral effects of all pharmacological agents are known. The aim of our investigation was to determine the effect of diclofenac on CBF velocity (CBFV) in patients with supratentorial pathology.

Methods and results

After obtaining approval from the Hospital Ethics Committee and written, informed consent, nine patients undergoing elective supratentorial neurosurgery were recruited. Patients were excluded if they had asthma, renal impairment, peptic ulcer disease, bleeding diathesis or had ingested NSAIDs within 24 h. No patient had signs of raised intracranial pressure.

The study was performed in the anaesthetic room before induction of anaesthesia. Patients were not premedicated and were kept in the supine position throughout the study period, with the head resting on a pillow. I.V. and arterial cannulae were inserted under local anaesthesia. Monitors included ECG, continuous arterial pressure, arterial blood gas sampling and axillary temperature.

CBFV was monitored continuously on the ipsilateral side of the intracerebral pathology. The M1 segment of the middle cerebral artery was insonated through the temporal window using a 2 MHz transcranial Doppler (TCD) ultrasound probe (Pioneer EME TCD VER 2.10, Eden Medical Electronics, Überlingen, Germany). The TCD probe was fixed in position to maintain a constant angle of insonation throughout the study. Confirmation of the middle cerebral artery was achieved by increasing sonation depth to visualization of the bidirectional flow pattern typical of the bifurcation of the internal carotid artery to the middle cerebral and anterior cerebral arteries. Insonation depth was then decreased to the point of maximum signal intensity (45–55 mm depth). The TCD frequency spectra, converted into flow velocity (cm s^{-1}), were calculated automatically by the TCD over 4–5 consecutive cardiac cycles.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Table 1 The effect of diclofenac on physiological variables Data are mean (SD) CBFV=cerebral blood flow velocity

	0 min (baseline)	15 min after diclofenac	40 min after diclofenac	*P*-value (40 min *vs* baseline)
Mean arterial pressure (mm Hg)	100 (11)	103 (10)	104 (8)	0.48
Heart rate (beats min^{-1})	62 (14)	61 (12)	61 (13)	0.94
Arterial oxygen pressure (mm Hg)	10.9 (1.2)	11.5 (1)	11.4 (0.8)	0.31
Arterial carbon dioxide pressure (mm Hg)	4.8 (0.2)	4.7 (0.3)	4.7 (0.4)	0.99
Temperature (°C)	36.3 (0.4)	not measured	36.2 (0.5)	0.78
Mean CBFV (cm s^{-1})	51.6 (11.7)	53.2 (12.6)	52.6 (11.7)	0.85
Systolic CBFV (cm s^{-1})	83.4 (14.7)	85.2 (16.6)	83.2 (15.8)	0.81

Measurements of baseline mean and systolic CBFV were recorded, along with mean arterial pressure, heart rate, temperature, and arterial oxygen and carbon dioxide pressures. Diclofenac, 75 mg in 50 ml normal saline, was then infused over 15 min. The i.v. route was chosen to avoid first-pass metabolism and provide a reliable peak plasma concentration. All measurements were repeated at the end of the infusion (time 15 min) and after a further 25 min (time 40 min), to coincide with the time of peak plasma concentrations.

Anaesthesia was then commenced and surgery continued as normal.

Data are expressed as mean (SD). Data from previous studies indicate that the mean value for CBFV is 65.55 (4.2) cm s^{-1} under normal physiological conditions.[3–6] A change of >2 SD was considered significant and with a power of 0.8, $\alpha=0.05$ and $\beta=0.2$, we calculated that eight subjects would be required.

Analysis of variance (ANOVA) for repeated measurements was used to compare the values. The changes from baseline to time 15 min and baseline to time 40 min following diclofenac administration were estimated separately. A value of $P<0.05$ was considered statistically significant.

Nine patients were recruited. The mean age was 49.6 (range 25–72) and the mean weight was 73.2 (13.8) kg. The effects of diclofenac on physiological variables are shown in Table 1. There was no statistical difference between measurements of CBFV at 15 and 40 min compared with baseline. No statistical differences were found between the physiological variables of mean arterial pressure, heart rate, temperature, and arterial oxygen and carbon dioxide pressures. Results of the tissue analysis in the nine volunteers revealed five gliomas, two astrocytomas, one lymphoma and one inflammatory tissue.

Comments

We find that diclofenac provides useful perioperative analgesia in a select group of neurosurgical patients but we were unsure of its effects on cerebral physiology. Animal studies have shown that diclofenac has no effect on cerebral haemodynamics but this had not been confirmed in humans, or in this patient population. The results of this study demonstrate that diclofenac does not cause significant changes in CBFV. We compared mean and systolic CBFV before and after the administration of diclofenac in patients with supratentorial pathology. Other physiological parameters that might have affected CBF remained constant. The patients were awake during the experiment and received no pharmacological agents other than diclofenac in normal saline 50 ml, thus avoiding potential alterations of CBF or intracerebral vessel diameter.

Indomethacin, another NSAID, is a potent cerebral vasoconstrictor. It decreases CBF by up to 40% without a change in cerebral metabolic rate, similar to the effects of hypocapnia. However, this effect appears to be unique among the NSAIDs. Its mechanism of cerebral vasoconstriction is still uncertain, but seems to result from mechanisms other than prostaglandin inhibition.[7] The role of NSAIDs in the management of cerebral injury has also been investigated. NSAIDs may improve collateral circulation in ischaemic brain and prevent cerebral vasospasm following subarachnoid haemorrhage.[8 9] Indomethacin has been used to control intracranial pressure and improve operating conditions in patients with cerebral tumours.[10]

We chose to study patients with intracerebral pathology as this may alter CBF and its regulation, and for the practical reason that this reflects our clinical patient population likely to receive diclofenac. As our numbers are small, we may have overlooked a significant response to diclofenac with a given tumour type, although no trend was seen.

Absolute CBF cannot be inferred from measurements of CBFV because the diameter of the insonated vessel segment is unknown. Despite this, the use of the TCD to measure CBFV has been shown to provide a good correlation between changes in flow velocity and cerebral blood flow as long as measurement conditions such as insonation angle and depth remain constant.[11]

In conclusion, we have shown that there is no significant change in CBFV after the administration of diclofenac in a small group of patients with supratentorial tumours.

References

1 Markus HS, Vallance P, Martin M, Brown M. Differential effect of three cyclooxygenase inhibitors on human cerebral blood flow velocity and carbon dioxide reactivity. *Stroke* 1994; **25**: 1760–64

2 Quintana A, Raczka E, Quintana MA. Effects of indomethacin and diclofenac on cerebral blood flow in hypercapnic conscious rats. *Eur J Pharmacol* 1988; **149**: 385–8

3 Eriksson S, Hagenfeldt L, Law D, Patrono C, Pinca E, Wennmalm A. Effect of prostaglandin synthesis inhibitors on basal and carbon dioxide stimulated cerebral blood flow in man. *Acta Physiol Scand* 1983; **117**: 203–11

4 Lee H-W, Caldwell JE, Dodson B, Talke P, Howley J. The effect of clonidine on cerebral blood flow velocity, carbon dioxide cerebral vasoreactivity, and response to increased arterial pressure in human volunteers. *Anesthesiology* 1997; **87**: 553–8

5 Larsen FS, Olsen KS, Hansen BA, Paulson OB, Knudsen GM. Transcranial Doppler is valid for determination of the lower limit of cerebral blood flow autoregulation. *Stroke* 1994; **25**: 1985–8

6 Dahl A, Russel D, Nyberg-Hansen R, Rootwelt K. Effect of nitroglycerin on cerebral circulation measured by transcranial Doppler and SPECT. *Stroke* 1989, **20**. 1733–6

7 Bedforth NM, Girling KJ, Skinner HJ, Mahajan RP. The effects of desflurane on cerebral autoregulation. *Br J Anaesth* 2001; **2**: 193–7

8 Phillis JW, Delong RE, Towner JK. Indomethacin and ibuprofen enhance anoxia-induced hyperaemia in rat brain. *Eur J Pharmacol* 1986; **124**: 85–91

9 Chyatte D. Prevention of chronic cerebral vasospasm in dogs with ibuprofen and high dose methylprednisolone. *Stroke* 1989; **20**: 1021–6

10 Bundgaard H, Jensen K, Cold GE, Bergholt B, Frederiksen R, Pless S. Effects of perioperative indomethacin on intracranial pressure, cerebral blood flow, and cerebral metabolism in patients subjected to craniotomy for cerebral tumors. *J Neurosurg Anaesth* 1996; **8**: 273–9

11 Bishop CCCR, Powell S, Rutt D, Browse NL. Transcranial doppler measurement of middle cerebral artery blood flow velocity. a validation study. *Stroke* 1986; **17**: 913–5

British Journal of Anaesthesia 89 (5) 764–6 (2002)

Sevoflurane and propofol decrease intraocular pressure equally during non-ophthalmic surgery and recovery

S. Sator-Katzenschlager[1, 2]*, E. Deusch[2], S. Dolezal[1], A. Michalek-Sauberer[1, 2], R. Grubmüller[1], G. Heinze[3] and A. Wedrich[4]

[1]Department of Anaesthesiology and General Intensive Care A, University of Vienna, Austria. [2]Department of Anaesthesiology and General Intensive Care B, University of Vienna, Austria. [3]Department of Medical Computer Science, University of Vienna, Austria. [4]Department of Ophthalmology and Optometrics, University of Vienna, Austria

**Corresponding author: Department of Anaesthesiology and General Intensive Care, University of Vienna, Währinger Gürtel 1820, A-1090 Vienna, Austria*

Background. To provide good control of intraocular pressure (IOP) during anaesthesia and surgery, we conducted a study comparing the effects on IOP during maintenance and recovery of sevoflurane *vs* propofol anaesthesia in 33 patients (ASA I–II) undergoing elective non-ophthalmic surgery.

Methods. Anaesthesia was induced with propofol 2 mg kg^{-1}, fentanyl 2 µg kg^{-1} and vecuronium 0.1 mg kg^{-1}. Patients were allocated randomly to receive either propofol 4–8 mg kg^{-1} h^{-1} (group P; n=16) or 1.5–2.5 vol% sevoflurane (group S; n=17) for maintenance of anaesthesia. Fentanyl 2–4 µg kg^{-1} was added if necessary. The lungs were ventilated with 50% air in oxygen. Blood pressure, heart rate, oxygen saturation and end-tidal carbon dioxide were measured before and throughout anaesthesia and in the recovery room. IOP was determined with applanation tonometry (Perkins) by one ophthalmologist blinded to the anaesthetic technique.

Results. There was a significant decrease in IOP after induction and during maintenance of anaesthesia in both groups. No significant differences in IOP between the two groups was found.

Conclusion. Sevoflurane maintains the IOP at an equally reduced level compared with propofol.

Br J Anaesth 2002; **89**: 764–6

Keywords: anaesthetics i.v., propofol; anaesthetics volatile, sevoflurane; analgesics opioid, fentanyl; eye, intraocular pressure

Accepted for publication: June 18, 2002

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

One goal of anaesthetic management during ophthalmic surgery is to provide good control of intraocular pressure (IOP). An increase in IOP may be catastrophic in patients with glaucoma or a penetrating open-eye injury. The IOP is determined by several factors, e.g. the rate of aqueous humour production, vitreous volume, choroidal blood volume, sclera rigidity, orbicularis oculi muscle tension and external pressure.[1] The normal IOP is approximately 15 mm Hg, with a normal range of 10–20 mm Hg. Previous studies have examined the effects of anaesthetics and related drugs on IOP, although the mechanisms underlying effects on IOP remain largely unclear. Potent inhalation anaesthetics are used widely for maintenance of general anaesthesia because of their ease of administration and practicable intraoperative and recovery characteristics.[2] Since the introduction of propofol, i.v. anaesthesia has also been used commonly. Sevoflurane and sevoflurane—remifentanil both decreased IOP from baseline values in rabbits, with no difference between groups.[3] No reports have been published concerning the effects of sevoflurane on IOP in humans. Therefore we performed a randomized, prospective, single-blinded study to compare the effects of sevoflurane and propofol on intraocular pressure during maintenance and recovery of anaesthesia.

Methods and results

After obtaining approval from the ethics committee of the hospital and written, informed consent, we studied 32 Caucasian patients aged 16–60 yr, ASA I or II, undergoing elective gynaecological or urological procedures. Exclusion criteria included a previous history of malignant hyperthermia, known allergies or adverse reaction to inhalation anaesthetics or propofol, patients with pre-existing ophthalmic diseases and those who had had laparoscopic surgical procedures. Patients were not envisaged to receive any catecholamine during the study.

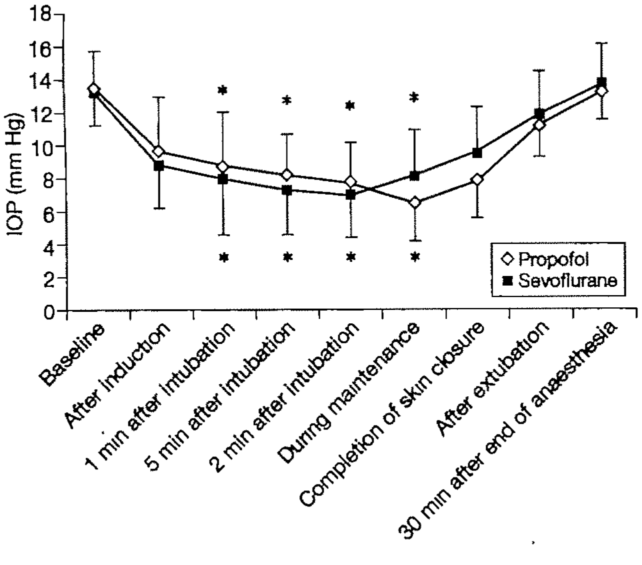


Fig 1 Intraocular pressure (IOP) in patients (n=33) undergoing non-ophthalmic surgery anaesthesia. Data are mean and SD $*P \leqslant 0.05$ compared with baseline values.

Patients were allocated randomly to one of two groups: group P (n=16) and group S (n=17). All patients received orally midazolam 7.5 mg as premedication 1 h before surgery. Anaesthesia was induced with fentanyl 2 μg kg^{-1} and propofol 2 mg kg^{-1}, and vecuronium 0.1 mg kg^{-1} was used to facilitate tracheal intubation. Ventilation was adjusted to maintain end-tidal carbon dioxide partial pressure ($P\text{E}'_{\text{CO}_2}$) at 4.3–4.6 kPa. Anaesthesia was maintained in group P with a continuous infusion of propofol 6–8 mg kg^{-1} h^{-1} and in group S with 1.5–2.5% sevoflurane All patients were ventilated with a 50% mixture of air and oxygen. The inspired concentration of sevoflurane or infusion rate of propofol was titrated to maintain mean arterial blood pressure (MAP) and heart rate (HR) within 20% of baseline values. Mean MAP, electrocardiography, HR, arterial oxygen saturation ($S\text{a}_{\text{O}_2}$), end-tidal carbon dioxide (E'_{CO_2} and nasopharyngeal temperature were measured continuously throughout anaesthesia. IOP values were obtained with a hand-held Perkins applanation tonometer.[4] Patients were positioned supine for examination. One ophthalmologist, blinded to the anaesthetic technique, made all IOP measurements. IOP was measured before induction of anaesthesia (baseline), after induction but immediately before intubation, 1 min after intubation, 5 min after intubation and 2 min after skin incision, then every 15 min during maintenance of anaesthesia, completion of skin closure and after tracheal extubation.The inspired sevoflurane concentration was reduced or discontinued to achieve an end-tidal sevoflurane concentration of <0.1% by the completion of skin closure. The propofol infusion was also discontinued before completion of skin closure. In the recovery room, 30 min after the end of anaesthesia, a final measurement of IOP and haemodynamic variables and $S\text{a}_{\text{O}_2}$ was performed.

Baseline values are presented as mean (SD) and compared using t-tests. ANOVA for repeated measurements was used to assess differences from baseline values within groups and differences between groups at specific time-points. $P<0.05$ was considered statistically significant, using the Bonferroni–Holm method. Randomization of the patients was achieved using a computer-generated table.

All patients were evaluated and were comparable in age, body weight, sex and duration of operation. After induction of anaesthesia there was a significant decrease in IOP compared with baseline values in both groups ($P<0.05$). During maintenance of anaesthesia, significant IOP reductions over time were found in both groups ($P<0.05$). After extubation, the IOP increased in group P and S and returned nearly to baseline values. In the recovery room 30 min after the end of anaesthesia, IOP had returned to baseline values in group P and S. No significant differences in IOP were found between the groups. The baseline values of IOP were also similar between the groups (Fig. 1). Baseline values of haemodynamic (MAP and HR) and respiratory (E'_{CO_2} and Sa_{O_2}) variables were similar between the groups. MAP did not decrease significantly from baseline after induction and maintenance of anaesthesia, but HR decreased significantly from baseline during anaesthesia in groups P and S (both $P<0.01$). The respiratory variables were stable thoughout in both groups. No significant differences in MAP or HR and E'_{CO_2} or Sa_{O_2} were found between groups. No correlation was found between MAP, HR and IOP values.

Comment

This study has demonstrated that during maintenance of anaesthesia significant IOP reductions occurred over time in both groups. During recovery from anaesthesia IOP returned to baseline values in both groups. No significant differences in IOP were found between the sevoflurane and propofol groups.

Apart from glaucoma, many factors influence intraocular pressure, such as genetics, age, refractive error and race.[1] Central venous pressure and arterial carbon dioxide tension may influence IOP also. Any acute rise in intra-abdominal or intrathoracic pressure, which are observed frequently during extubation, might increase IOP. Particular attention must be paid to induction and emergence of anaesthesia, as both mechanical and pharmacological stressors have an amplifying effect on IOP. Most anaesthetic and hypnotic agents, including potent inhalation anaesthetics, barbiturates, opioids, neuroleptics and benzodiazepines, decrease IOP in proportion to the depth of anaesthesia. Jantzen emphasized the importance of anaesthetic drugs when general anaesthesia was planned for ophthalmic surgery.[5]

Anaesthesia for eye surgery patients must prevent an increase in IOP. Our results suggest that sevoflurane is a practical maintenance agent for adults, which decreased the IOP during anaesthesia at a constantly low level in patients undergoing non-ophthalmic surgery. We have shown previously a decrease in IOP after anaesthetic maintenance with propofol.[6] The decrease in IOP after anaesthetic induction was sustained whether maintenance was provided by sevoflurane or propofol. In all groups, IOP increased towards baseline values after emergence from anaesthesia.

We conclude that maintenance of anaesthesia with sevoflurane sustained a low IOP at a level equivalent to that of propofol.

References

1 Cunningham AJ, Barry P. Intraocular pressure physiology and implications for anaesthetic management. *Can Anaesth Soc J* 1986; **33**: 195–208

2 Thomson MF, Brock-Utne JG, Bean P, Welsh N, Downing JW. Anaesthesia and intraocular pressure: a comparison of total intravenous anaesthesia using etomidate with conventional inhalation anaesthesia. *Anaesthesia* 1982; **37**: 758–61

3 Artru AA, Momota Y. Trabecular outflow facility and formation rate of aqueous humor during anesthesia with sevoflurane nitrous oxide or sevoflurane–remifentanil in rabbits. *Anesth Analg* 1999; **88**: 781–6

4 Dunn R, Brubaker F. Perkins applanation tonometer, clinical and laboratory evaluation. *Arch Ophthalmol* 1973; **89**: 149–51

5 Jantzen JPAH. Anaesthesia and intraocular pressure. *Anaesthesist* 1988; **37**: 458–69

6 Sator S, Wildling E, Schabernig C, Akramian J, Zulus E, Winkler M. Desflurane maintains intraocular pressure at an equivalent level to isoflurane and propofol during unstressed non-ophthalmic surgery. *Br J Anaesth* 1998; **80**: 243–4

British Journal of Anaesthesia 89 (5) 766–9 (2002)

Atracurium is associated with postoperative residual curarization

C. McCaul, É. Tobin, J. F. Boylan and A. J. McShane*

Department of Anaesthesia, Intensive Care and Pain Medicine, St Vincent's University Hospital, Elm Park, Dublin 4, Ireland

**Corresponding author*

Background. Residual paralysis following the use of neuromuscular blocking drugs remains a clinical problem. As part of departmental quality assurance, we examined the degree of postoperative residual curarization (PORC) following atracurium.

Methods. Forty patients undergoing general anaesthesia involving atracurium were studied. Quantitative neuromuscular monitoring (mechanomyography, Myograph 2000, Biometer, Denmark) was performed by assessing the response to supramaximal train-of-four (TOF) stimulation of the ulnar nerve. Anaesthesia was provided by non-participating clinicians who were blinded to the study data. A TOF ratio ≤ 0.7 at extubation was classified as PORC.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Results. At antagonism of neuromuscular block, 70% (28/40) of patients had a TOF ratio ≤0.7, and 65% (26/40) of patients had a TOF ratio ≤0.7 at extubation. Peripheral nerve stimulator use was associated with a longer interval from antagonism of block to extubation (P=0.01), but was not associated with differences in atracurium dosage or a reduction in PORC at extubation. Patients with TOF ratio ≤0.7 at extubation had surgery of shorter duration [59 (SEM 6) *vs* 103 (9) min, P<0.001], greater doses of atracurium relative to the duration of surgery [6 (1) *vs* 11 (1) μg kg^{-1} min^{-1}, P<0.005], and shorter intervals from administration of last dose of atracurium to antagonism of neuromuscular block [29 (2) *vs* 53 (9) min, P<0.005] and from antagonism to extubation [6 (1) *vs* 15 (4) min, P<0.01]. Duration of surgical procedure was the sole multivariate predictor of PORC [odds ratio 0.94 (95% confidence intervals 0.91–0.98), P<0.01].

Conclusions. PORC remains a clinical problem despite use of intermediate-duration neuromuscular blocking drugs and peripheral nerve stimulators. Patients undergoing procedures of short duration may be at risk of inappropriately early tracheal extubation, possibly due to work pressures. The association between suboptimal antagonism of neuromuscular blockade and short procedures needs reinforcement during postgraduate training and departmental quality assurance.

Br J Anaesth 2002; **89**: 766–9

Keywords: anaesthesia; complications, morbidity; complications, postoperative; neuromuscular block, atracurium

Accepted for publication: July 3, 2002

Residual postoperative paralysis following use of neuromuscular blocking drugs may result in morbidity and mortality.[1 2] Residual paralysis resulting from absent or incomplete antagonism of competitive neuromuscular blockade is known as postoperative residual curarization (PORC). Recent literature suggests that PORC remains a problem.[3]

As part of departmental quality assurance, we examined the incidence and degree of PORC associated with the use of the intermediate-duration neuromuscular blocking agent, atracurium at: (i) antagonism of block, (ii) extubation, and (iii) in the recovery area. The study also examined factors contributing to PORC, such as drug dosage, timing of drug administration, duration of surgery, experience of anaesthetists and use of peripheral nerve stimulators.

Methods and results

Following approval by the hospital research ethics committee, informed consent was obtained from 40 ASA I elective surgical patients [age 38 (19–63) yr] who were scheduled to undergo general anaesthesia with tracheal intubation, muscle relaxation and mechanical ventilation. The surgical procedures involved were abdominal (20), breast (6), varicose veins (6), and miscellaneous (8).

Premedication, induction technique, neuromuscular blocking drug dosage and antagonism, maintenance agents, neuromuscular monitoring and timing of extubation were chosen by the anaesthetist controlling the case. Only patients who were to receive atracurium were included in the study.

Train-of-four (TOF) ratio (TOFR) monitoring was continuous and was recorded from induction of anaesthesia to extubation, which took place in the operating theatre The mechanical response of adductor pollicis was measured using a force displacement transducer (Myograph 2000, Biometer, Denmark). After induction, but before administration of the neuromuscular blocking drug, a stable baseline was established. TOF stimulation was then assessed at 10-s intervals by stimulation of the ulnar nerve with four impulses at 0.5-s intervals, duration 0.2 ms and current 60 mA. PORC was judged to be present when the ratio of the twitch height of the fourth impulse to the height of the first (TOFR) was ≤0.7. Myographic data recordings were not available to the responsible clinical anaesthetists, but peripheral nerve stimulators were. After tracheal extubation, patients were observed continuously in the operating theatre and the recovery room for clinical signs and symptoms of PORC.

Data are presented as frequencies or means (SEM) as appropriate. A Student's t-test was used to analyse patient characteristics and to compare the patients with and without PORC. The chi-squared test was used to analyse the incidence of peripheral nerve stimulator use and clinical problems. Logistic regression was used for multivariate analysis.

Twenty-six (65%) patients had a TOFR ≤0.7 at extubation (Table 1). Compared with patients with a

TOFR >0.7, patients with a TOFR ≤0.7 at extubation had had shorter procedures ($P<0.001$), and more profound neuromuscular block at the time of neostigmine administration. Patients with residual paralysis (TOFR ≤0.7 at extubation) had significantly shorter time intervals from administration of last dose of atracurium to administration of antagonist [29 (2) *vs* 53 (9) min, $P<0.001$] and from administration of antagonist to extubation [6 (1) *vs* 15 (4) min, $P=0.01$]. TOFR at the time of antagonism was positively correlated with time elapsed since last dose of atracurium ($r^2=0.57$, $F=50.4$, $P=0.0001$).

After extubation, 19 patients had clinical evidence of impaired neuromuscular function as evidenced by a total of 40 clinical events. These comprised uncoordinated movements, oxygen desaturation, upper airway obstruction, ptosis and diplopia/blurring of vision. Of these patients, 18/19 had a TOFR <0.7 at extubation. The episodes of desaturation and obstruction were treated successfully with increased concentrations of inspired oxygen and airway manipulation. A further dose of neostigmine was administered to one patient in the recovery room after the anaesthetist observed uncoordinated movements.

A peripheral nerve stimulator was used in 50% (20/40) of patients. Trainees who did not use nerve stimulators were more experienced than those who did [6.3 (0.8) *vs* 4.5 (0.4) yr, $P=0.04$]. Use of nerve stimulators was not associated with altered atracurium dosage, depth of blockade before antagonism, time interval from antagonism of neuromuscular block to tracheal extubation, or incidence of PORC.

The sole multivariate predictor of residual neuromuscular block was duration of surgical procedure, which correlated inversely with PORC [odds ratio 0.94 (95% confidence interval 0.91–0.98), $P<0.01$].

Table 1 Patient characteristics, neuromuscular block, antagonism, and clinical signs of postoperative residual curarization, characterized by train-of-four ratio (TOFR) at extubation. Values are absolute (*n*) or mean (SEM). ****$P<0.0001$, ***$P<0.001$; **$P<0.005$, *$P<0.05$

	TOFR at extubation	
	>0.7	≤0.7
Number (*n*)	14	26
Weight (kg)	75 (3)	70 (2)
Male/female (*n*)	8/6	14/12
Duration of surgery (min)	103 (9)	59 (6)***
Anaesthetists' experience (yr)	5.8 (0.8)	4.8 (0.5)
Total atracurium dosage (μg kg^{-1}min^{-1})	6 (1)	11 (1)**
Neostigmine (μg kg^{-1})	43(5)	40 (3)
Nerve stimulator use (*n*)	6	14
Time from last dose of atracurium to antagonism of block (min)	53 (9)	29 (2)***
Time from last dose of atracurium to extubation (min)	68 (9)	35 (2)****
Time from antagonism of block to extubation (min)	15 (4)	6 (1)**
TOFR at reversal	0.40 (0.10)	0.01 (0.01)****
TOFR at extubation	0.93 (0.02)	0.24 (0.04)****
Ptosis (*n*)	0	11
Diplopia/blurred vision (*n*)	1	8
Failed sustained head lift (*n*)	0	8
Uncoordinated movements (*n*)	0	7
Oxygen desaturation (*n*)	0	2
Upper airway obstruction (*n*)	0	2

Comment

In patients emerging from general anaesthesia, we found a high incidence of curarization at the time of tracheal extubation, with many patients having significant residual neuromuscular block on clinical testing in the recovery room. This occurred despite the use of an intermediate-duration neuromuscular blocking drug, frequent (though not universal) use of peripheral nerve stimulator monitoring, and routine use of pharmacological antagonism. The incidence of PORC at the time of extubation observed in this study is higher than that reported in other studies.[3–5] In our study, we assessed the TOFR at the time of extubation whilst in the majority of other studies, neuromuscular assessment was done in the postoperative care unit,[3–5] at time intervals exceeding the recovery index of atracurium,[6] thus allowing greater recovery of neuromuscular function.

PORC remains a problem even in carefully conducted clinical trials when the short-acting agent mivacurium is used and routinely antagonized.[7] In many patients in our study, the degree of neuromuscular block was profound at the time of antagonism, with many patients having a TOFR of zero, demonstrating low levels of spontaneous recovery from neuromuscular block.

The attempted antagonism of deep levels of neuromuscular blockade may reflect the pressure on anaesthesia providers to turn over cases rapidly, and increased reliance on the skills and services of recovery personnel in order to meet these time demands.[8] In support of this hypothesis, PORC was associated with shorter procedures and shorter intervals from administration of an antagonist to extubation. TOFR at antagonism was directly related to time elapsed since the last dose of atracurium.

We speculate that a level of complacency exists with regard to usage of intermediate-duration neuromuscular blocking agents. Contemporary audit data from France,[3] Belgium,[4] and Northern Ireland[5] report incidences of PORC in the recovery room of 30–64%, although many instances occurred in patients who did not receive an anticholinesterase. The data from our series suggest that there is an assumption that routine use of an anticholinesterase guarantees adequate antagonism of neuromuscular block, and may explain the relatively low use of peripheral nerve stimulators. Complacency may also exist because, although strong outcome data have established that PORC after the use of pancuronium is associated with postoperative pulmonary complications,[1] substantial evidence has yet to be accrued for atracurium or vecuronium. Despite the availability of peripheral nerve stimulators, they are frequently not employed and even in experienced hands may not detect PORC.

Our study has obvious limitations. While atracurium was used in all patients, its mode of use and the conduct of the anaesthesia, including temperature measurement and regulation, was entirely at the discretion of the responsible anaesthetist. Since our study was carried out it has been demonstrated that pharyngeal constrictor function is not normalized until recovery of an adductor pollicis TOF>0.9.[9] Thus the previously accepted parameter of 0.7 may be inappropriate.

In conclusion, we have found that PORC is still a clinical problem despite the use of intermediate-duration neuromuscular blocking drugs and their routine antagonism. The association between suboptimal antagonism and both relatively short procedures and a short interval between antagonism of neuromuscular block and extubation needs to be reinforced during postgraduate training and departmental quality assurance.

Acknowledgement

É. Tobin and A. McShane were supported by the Health Research Board (Ireland).

References

1 Berg H, Roed J, Viby-Mogensen J, *et al.* Residual neuromuscular block is a risk factor for postoperative pulmonary complications. A prospective, randomized, and blinded study of postoperative pulmonary complications after atracurium, vecuronium and pancuronium. *Acta Anaesthesiol Scand* 1997; **41**: 1095–103

2 Lunn JN, Hunter AR, Scott DB. Anaesthesia-related surgical mortality. *Anaesthesia* 1983; **38**: 1090–6

3 Baillard C, Gehan G, Reboul-Marty J, Larmignat S, Samana CM, Cupa M. Residual curarization in the recovery room after vecuronium. *Br J Anaesth* 2000; **84**: 394–5

4 Fezing AK, d'Hollander A, Boogaerts JG. Assessment of the postoperative residual curarisation using the train of four stimulation with acceleromyography. *Acta Anaesthesiol Belg* 1999; **50**: 83–6

5 Hayes AH, Mirakhur RK, Breslin DS, Reid JE, McCourt KC. Postoperative residual block after intermediate-acting neuromuscular blocking drugs. *Anaesthesia* 2000; **56**: 312–18

6 Basta SJ, Ali HH, Savarese JJ, *et al.* Clinical pharmacology of atracurium besylate (BW 33A): A new non depolarizing muscle relaxant. *Anesth Analg* 1982; **68**: 723–32

7 Bevan DR, Kahwaji R, Ansermino JM, *et al.* Residual block after mivacurium with or without edrophonium reversal in adults and children. *Anesthesiology* 1996; **84**: 362–7

8 Gaba DM, Howard SK, Jump B. Production pressures in the work environment: California anesthesiologists' attitudes and experiences. *Anesthesiology* 1994; **81**: 488–500

9 Eriksson LI, Sundman E, Olsson R, *et al.* Functional assessment of the pharynx at rest and during swallowing in partially paralyzed humans: simultaneous videomanometry and mechanomyography of awake human volunteers. *Anesthesiology* 1997; **87**: 1035–43

British Journal of Anaesthesia **89** (**5**): 769–71 (2002)

Effects of prolonged head-down tilt on internal jugular vein cross-sectional area

S. J. Schreiber*, U. K. W. Lambert, F. Doepp and J. M. Valdueza

Department of Neurology, University Hospital Charité, Schumannstrasse 20/21, D-10098 Berlin, Germany
**Corresponding author*

Background. Head-down tilt is often used to assist cannulation of the internal jugular vein (IJV). However, the optimal duration of tilt before cannulation is not well defined.

Methods. Fifteen healthy volunteers were studied by B-mode duplex sonography to assess changes in cross-sectional area (CSA) of the right IJV during 10° head-down tilt.

Results. Median CSA in the supine position was 102 mm^2 [range 16–266, mean (SD) 113 (69)]. CSA increased to 139 mm^2 [23–388, 158 (93)] immediately after tilting ($P<0.0001$, repeated measures ANOVA). No significant further change was noted in the next 20 min. CSA returned to baseline level after return to the supine position.

Conclusion. The 10° head-down tilt manoeuvre in healthy volunteers causes an immediate, significant increase in CSA in the right IJV. A longer tilt did not cause further increase in jugular CSA.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Br J Anaesth 2002; **89**: 769–71

Keywords: measurement techniques, B-mode ultrasound; position, head-down tilt manoeuvre; veins, jugular, cannulation

Accepted for publication: June 24, 2002

Internal jugular vein (IJV) cannulation for inserting a central venous catheter is used frequently in patients during major surgery and intensive care. Better conditions for venous cannulation and the reduction of complications are continuing concerns. Methods such as head-down tilt of varying extent,[1–3] the Valsalva manoeuvre,[2 4] hepatic compression[5 6] and positive intrathoracic pressure in ventilated patients[5 6] have been proposed to increase jugular filling. The most commonly recommended approach is ultrasound guidance during head-down tilt with the head rotated <40°.[7 8] We studied changes in right jugular cross-sectional area (CSA) with time during prolonged tilt, to determine the best time for cannulation. Values are given as mean (SD).

Methods and results

Nineteen healthy volunteers (eight women and 11 men; age range 23–68 yr) were studied. The CSA of the right IJV was assessed by B-mode duplex sonography using a 7.5–9 MHz longitudinal transducer (Powervision 6000, SSA-370A, Toshiba, Tokyo, Japan). The probe was placed in a horizontal plane, 1.5 cm caudal to the cricoid cartilage, corresponding to the most frequently used point of needle insertion into the IJV. The examination started in the supine position with the head slightly extended and rotated about 20–30° to the contralateral side. After 3 min of baseline recording, the subject was placed 10° head-down for 20 min, after which there was another 3 min assessment in the supine position. Short video sequences were stored on SVGA videotape every minute and off-line measurements of the pulse-triggered minimal right jugular CSA were made using the manual area trace function of the duplex machine (Fig. 1).

For statistical analysis, non-parametric repeated measures ANOVA (Friedman's test) and Dunn's multiple comparison post test were performed. $P<0.05$ was considered significant.

The median jugular CSA in the supine position before head-down tilt was 102 mm^2 [range 16–266, mean 113 (69)]. One minute after tilting the median area had increased to 139 mm^2 [range 23–388, mean 158 (93)] and did not change significantly in the next 20 min. On return to the supine position, CSA values immediately returned to baseline levels (Fig. 2).

Comment

Head-down tilt is often used to improve cannulation of the IJV. Jugular diameter or CSA in adults increases on ultrasound, with varying degrees of tilt. Armstrong and colleagues demonstrated a rising lateral IJV diameter with 10, 20 and 30° of head-down tilt, the greatest change (+14%) occurring between the supine and the 10° tilt position.[2] In 15 patients during anaesthesia, mean right jugular CSA of 160 (86) mm^2 when supine increased to 213 (112) mm^2 with 10° tilt (relative increase +25%).[6] CSA increased by 37% (from 118 to 162 mm^2 during head-down tilt) in ICU patients.[3] Our finding of an approximately 36% increase therefore supports the data previously published.

A recent study, providing information about the duration of tilt, reported a baseline CSA of 95 (26) mm^2 and follow-up values of 118 (39) and 116 (43) mm^2 after 1 and 10 min of tilt respectively.[1] We found that the venous CSA changes

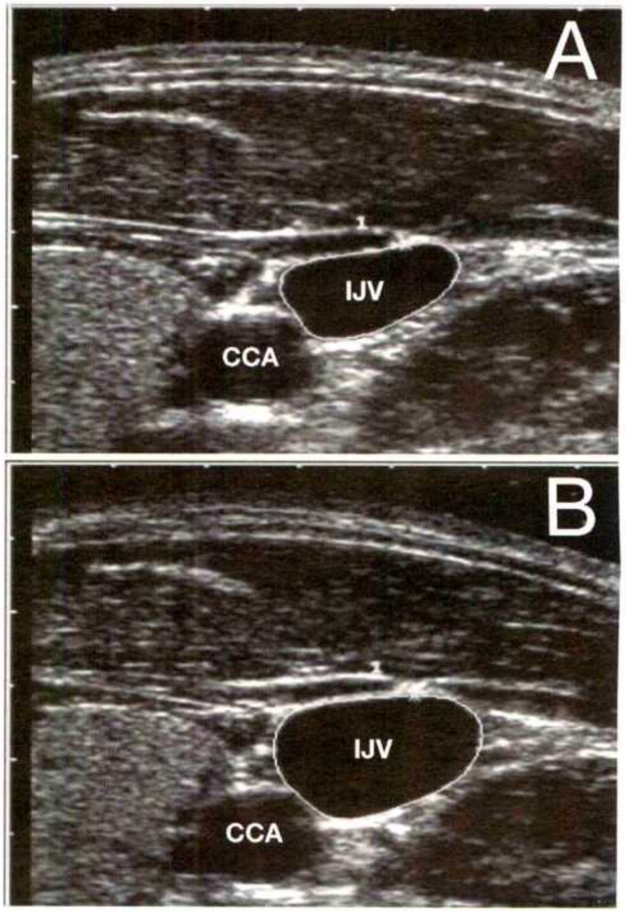


Fig. 1 Cross-sectional B-mode ultrasound scan. (A) Right IJV. CSA of a subject in the supine position; area 43.9 mm^2. (B) CSA in the same subject during 10° head-down tilt; area 73.2 mm^2. CCA = common carotid artery.

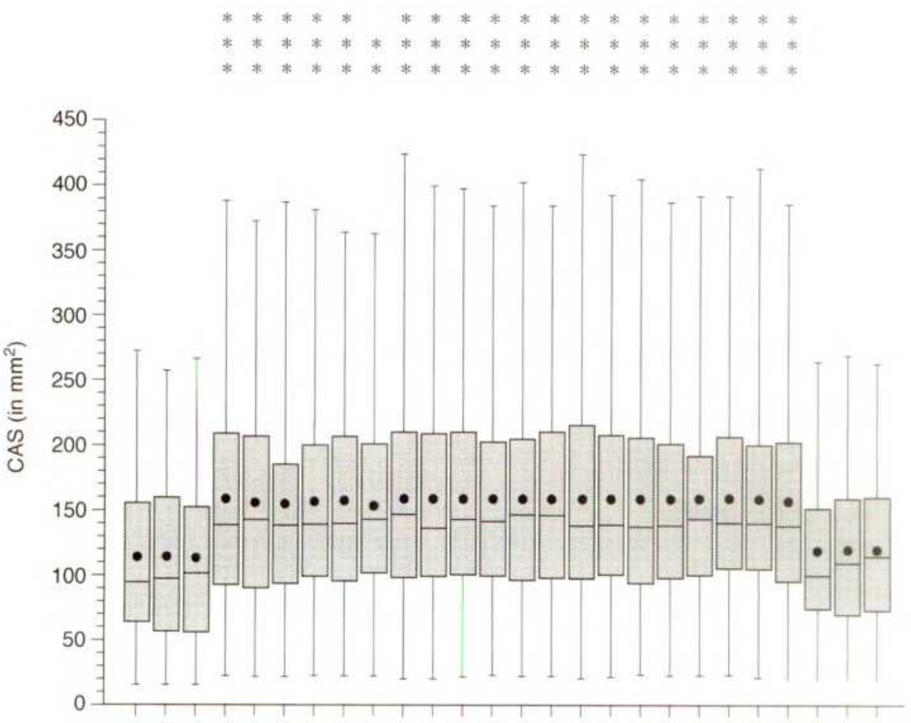


Fig 2 Box plot analysis of results including mean (dot), median (horizontal bar within box), 25th and 75th percentiles (box) and minimal/maximal values (whisker). Time course of jugular CSA changes at baseline (supine position, s1–s3), during 20 min of 10° head-down tilt (tilt position, t4–t23) and upon return to baseline position (s24–s26). Statistical comparison between groups (Dunn's test): s3 *vs* t4–t23: $^{**}P<0.01$, $^{***}P<0.001$.

occurred within 1 min after head-down positioning. During the following 19 min, however, no further change in mean jugular CSA was found.

To assess if the individual change differed from the median results, each case was analysed for the time at which the maximal CSA was detected. Interestingly, we found a nearly even time distribution, with a median duration of 8 min (range 1–20). However, the absolute differences between the 1 min and maximal CSAs compared with the differences during the 3 min supine measurements (i.e. the systematic error of the applied ultrasound method) gave median values of 10 mm^2 [range 0–37, mean 12 (10)] and 8 mm^2 [range 0–16, mean 8 (5)] respectively. The remaining real increase in mean area of 2 mm^2 during 20 min of head-down tilt compared with a 37 mm^2 increase after 1 min of tilt is small and clinically irrelevant.

Prolongation of a position that can be uncomfortable for conscious patients is unnecessary.

Acknowledgement

The study was supported by a grant from the Schering Forschungsgesellschaft mbH, Berlin, Germany.

References

1 Terai C, Anada H, Matsushima S, Shimizu S, Okada Y. Effects of mild Trendelenburg on central hemodynamics and internal jugular vein velocity, cross-sectional area, and flow. *Am J Emerg Med* 1995; **13**: 255–8

2 Armstrong PJ, Sutherland R, Scott DH. The effect of position and different manoeuvres on internal jugular vein diameter size. *Acta Anaesthesiol Scand* 1994; **38**: 229–31

3 Mallory DL, Shawker T, Evans RG *et al.* Effects of clinical maneuvers on sonographically determined internal jugular vein size during venous cannulation. *Crit Care Med* 1990; **18**: 1269–73

4 Lobato EB, Sulek CA, Moody RL, Morey TE. Cross-sectional area of the right and left internal jugular veins. *J Cardiothorac Vasc Anesth* 1999; **13**: 136–8

5 Verghese ST, Nath A, Zenger D, Patel RI, Kaplan RF, Patel KM. The effects of the simulated Valsalva maneuver, liver compression, and/or Trendelenburg position on the cross-sectional area of the internal jugular vein in infants and young children. *Anesth Analg* 2002; **94**: 250–4

6 Lobato EB, Florete OG Jr, Paige GB, Morey TE. Cross-sectional area and intravascular pressure of the right internal jugular vein during anesthesia: effects of Trendelenburg position, positive intrathoracic pressure, and hepatic compression. *J Clin Anesth* 1998; **10**: 1–5

7 Docktor B, So CB, Saliken JC, Gray RR. Ultrasound monitoring in cannulation of the internal jugular vein: anatomic and technical considerations. *Can Assoc Radiol J* 1996; **47**: 195–201

8 Sulek CA, Gravenstein N, Blackshear RH, Weiss L. Head rotation during internal jugular vein cannulation and the risk of carotid artery puncture. *Anesth Analg* 1996; **82**: 125–8

British Journal of Anaesthesia **89 (5)**: 772–4 (2002)

Posture used by anaesthetists during laryngoscopy[†]

J. D. Walker

Department of Anaesthesia, Ysbyty Gwynedd, Bangor LL57 2PW, UK

Background. There is little advice on the posture to be used when intubating the trachea. Does the stance used depend on experience?

Methods. Twenty-six subjects with varying experience of intubation were photographed during laryngoscopy of an intubation training mannequin. Posture was measured from the photographs and the data were analysed with the Mann–Whitney *U*-test.

Results. The less experienced group had shallower lines of sight, levered more, and stood with their face closer to the mannequin (*P*=0.037, 0.018 and 0.06 respectively).

Conclusions. Novice anaesthetists should be given explicit instructions on correct trolley height and should be taught to intubate with a straight back.

Br J Anaesth 2002; **89**: 772–4

Keywords: anaesthetic techniques, anaesthetist, posture; education, junior staff; equipment, mannequin

Accepted for publication: June 24, 2002

When acquiring a new skill, the correct posture is often taught first. Piano teachers are very strict on how we should sit and skiing instructors are equally firm on how we should stand. However, there is little guidance on the posture needed for laryngoscopy and intubation. This study determined whether there are differences in the way more experienced anaesthetists stand when intubating patients, and if this information could lead to advice for those learning to intubate.

Method and results

Twenty-six subjects with varying experience of laryngoscopy were photographed during laryngoscopy of a commonly used intubation mannequin, the Laerdal Airway Management Trainer (Laerdal Medical Corp., Wappingers Falls, NY, USA). The mannequin was placed on a trolley at a fixed height with a single pillow under the head. Participants were asked to visualize the larynx in the normal way, with a size 3 Macintosh laryngoscope. Once they had done so, they were told to hold a stylette along their line of sight. A photograph was taken using a tripod-mounted 35 mm camera placed 2 m directly to the right of the mannequin. The camera, trolley and mannequin were kept in the same position throughout the study. Calibration photographs were taken at regular intervals by photographing a ruler held in the mannequin's sagittal plane, to ensure that no movement had occurred. This also provided a method for converting measurements taken from the photographs into actual distances.

The following measurements were taken from the photographs (Fig. 1): (A) the angle between the line of sight and the horizontal; (B) the angle between the line of sight and the handle of the laryngoscope (upper edge); (C) the angle between the handle of the laryngoscope and the horizontal; and (D) the distance between the eye and the heel of the laryngoscope. In all cases the base of the training mannequin was taken as horizontal.

The subjects were divided into two groups according to seniority and the data were analysed with the Mann–Whitney *U*-test. $P < 0.05$ was considered significant. Basic statistical calculations were done with Microsoft Excel 2000, while Mann–Whitney *U*-tests were done manually.

Twenty-six subjects took part in the study. One subject was removed from the study on the grounds that he was a significant outlier: he was more than two standard deviations below the mean eye-to-laryngoscope distance and more than three standard deviations below the mean of the experienced group, to which he was allocated. The remain-

---

[†] This work has been presented to the Liverpool Society of Anaesthetists at the Registrars' Prize Competition 2002. It was awarded first prize.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

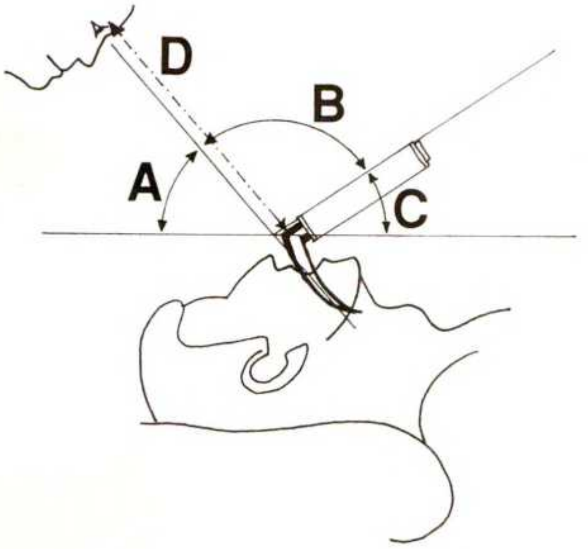


Fig 1 Angles and distances measured from photographs. A is the angle between the line of sight and the horizontal, B is the angle between the line of sight and the handle of the laryngoscope, C is the angle between the handle of the laryngoscope and the horizontal, and D is the distance between the heel of the laryngoscope and the eye.

der were allocated to a more experienced or less experienced group (Table 1). All participants were able to see the glottis. The less experienced group had significantly shallower lines of sight (A) [experienced group, mean (SD) 41.2 (4.8)°; less experienced group, 37.9 (4.2)°; $P<0.05$; overall range 31–51°]. The more experienced group levered less, with significantly lower laryngoscope handle angles (C) [experienced group, mean 36.6 (5.5)°; less experienced group, 44.1 (7.0)°; $P<0.05$; overall range 29–57°]. Eye-to-laryngoscope distances (D) were greater in the more experienced group, but the difference did not reach significance [experienced group, 35.6 (9.8) cm; less experienced group, 27.4 (8.7) cm; $P>0.05$; overall range 19–57 cm]. The angle of the line of sight to the laryngoscope handle was similar in the two groups, and showed a smaller overall range than other measurements [100.4 (3.7)°, range 92–107°]. There was no correlation between line of sight and eye-to-laryngoscope distance.

Comment

These results may not surprise many anaesthetists. Similar work by Matthews and Johnson[1] showed that experienced anaesthetists adopted a more erect posture, with the forearm closer to the horizontal and the anaesthetist's face further from the patient.

One of the most interesting aspects of this study is the limited range of the angle between the laryngoscope handle and the line of sight, which is readily explained by the design of the laryngoscope. Juniors are told not to lever and are warned of broken teeth. These data demonstrate that by levering they also lower their line of sight, hence making it more difficult to see.

Table 1 Details of the participants and group allocation

Group	Number of subjects
More experienced group	
Consultants	11
Post-fellowship registrars	3
Staff grade	3
Total	17
Less experienced group	
Specialist registrars	1
Senior house officers	3
Nurses	4
Total	8

A lower line of sight caused by levering in turn requires a reduction in height on the part of the anaesthetist. The less experienced group compensated with the upper body, by stooping and bringing their face closer to the patient. This may reduce binocular vision, as noted by Matthews and Johnson.[1] The more experienced group compensated for height with the lower body, by bending their knees or using a similar manoeuvre. One experienced subject compensated by bending his torso laterally, something the author had not seen before.

The poor correlation between low line of sight and low eye-to-laryngoscope distance was disappointing, because the lower sight-line should lead to stooping. However, a major confounding factor was the fixed height of the trolley, which was necessary because of the fixed position of the camera.

Correct trolley height is another factor on which very little is known. Otto[2] suggests having the patient's head between the anaesthetist's xiphisternum and umbilicus. The author suggests having the trolley surface at the same level as the anaesthetist's anterior superior iliac spines, which results in a similar position.

This study has other defects, apart from the fixed trolley height. The Laerdal Airway Management Trainer is a popular training mannequin, but is not the same as a real subject. It is much less compliant and is more difficult to intubate. Its stiffness means that it is very difficult to intubate on two pillows, as most anaesthetists normally would. However, it gave a 'standard' intubation model, which was identical for all subjects.

Presbyopia was not considered in the study design. However, most of the participants were quite young, so eyesight should not confound the data too much. The decision to remove one of the participants is controversial, but justified on the grounds that a study as small as this would be extremely sensitive to outliers. The criticism that a forced dichotomy has been created between 'more' and 'less' experienced groups is possibly valid; a better design would have been to study consultants against junior SHOs (senior house officers). However, the limited numbers of participants prevented this.

In spite of the shortfalls, some conclusions are justified. All anaesthetists should place the trolley at the correct height. Juniors should intubate with their back straight and should be taught to manipulate the line of sight by levering less instead of 'chasing' the sight-line by stooping. In situations where the trolley height is fixed, compensation for height should occur with the lower body.

References

1 Matthews AJ, Johnson CJH, Goodman NW. Body posture during simulated tracheal intubation. *Anaesthesia* 1998; **53**: 331–4

2 Otto CW. Tracheal intubation. In: Nunn JF, Utting JE, Brown BR, eds. *General Anaesthesia.* London: Butterworths, 1989; 512–39

British Journal of Anaesthesia **89** (**5**): 775–8 (2002)

BJA

CASE REPORTS

Air embolism: diagnosis with single-photon emission tomography and successful hyperbaric oxygen therapy

L. Droghetti[1]*, M. Giganti[2], A. Memmo[1] and R. Zatelli[1]

[1]*Department of Anaesthesia and Intensive Care Medicine, S. Anna Hospital, I-44100 Ferrara, Italy,*
[2]*Department of Nuclear Medicine, University of Ferrara, Ferrara, Italy*
**Corresponding author*

Venous air embolism may occur when the surgical field is above the level of the heart. We present a case of venous air embolism in a patient undergoing percutaneous nephrolithotripsy in the prone position and presenting with blindness and neurological deficits 8 h later. The clinical diagnosis of paradoxical air embolism was confirmed by early single-photon emission tomography (SPET), whereas magnetic resonance imaging including diffusion-weighted imaging (DW-MRI) was diagnostic only 30 h later. Hyperbaric oxygen therapy was successful. In this case, early DW-MRI scan was inconclusive, but a SPET study of the brain appeared to be useful in confirming the clinical diagnosis. Early hyperbaric oxygen was demonstrated to be a successful therapy.

Br J Anaesth 2002; **89**: 775–8

Keywords: anaesthesia, urology; complications, air embolism; therapy, hyperbaric oxygen

Accepted for publication: July 4, 2002

During surgical procedures in which the surgical field is positioned above the level of the heart, venous air embolism may occur. When the air passes through to the arterial system, causing paradoxical air embolism, the consequences can be devastating. We present a case of venous air embolism occurring in percutaneous nephrolithotripsy in the prone position, with features of paradoxical air embolism appearing 8 h later.

Case report

A previously healthy 36-yr-old male, height 175 cm, weight 84 kg, was scheduled for nephrolithotripsy for an upper pole staghorn calculus. Anaesthesia was induced with alfentanil 7 μg kg^{-1} and propofol 2 mg kg^{-1} i.v., and neuromuscular block was achieved with vecuronium bromide 0.1 mg kg^{-1}. After tracheal intubation with a cuffed tube, artificial ventilation was started and anaesthesia maintained with 60% nitrous oxide in oxygen and sevoflurane at an end-expiratory concentration of 1.5 vol%. Continuous intra-operative monitoring included an electrocardiogram (ECG), pulse oximetry (Sp_{O_2}), end-tidal carbon dioxide concentration (PE'_{CO_2}), end-tidal volatile anaesthetic agent concentration, and ventilation volumes and pressures, while non-invasive blood pressure was measured at 3-min intervals. Cystoscopy was performed and a catheter was inserted into the right ureter. The patient was then placed in the prone position with his head and legs down. A nephroscope connected to an ultrasound generator (Calculson-Storz, Tuttlingen, Germany) at 26 000 Hz was inserted into the renal pelvis, which was perfused constantly with saline solution flowing from an irrigating bag placed 40 cm above the surgical field and drained by an aspirating pump. About 10 min after the beginning of ultrasound lithotripsy, the PE'_{CO_2}decreased abruptly from 4 to 2.9 then to 1.8 kPa. The Sp_{O_2} decreased from 100 to 86% and the systolic arterial pressure from 120 to 96 mm Hg. The heart rate decreased from 75 to 60 beats min^{-1}. As the airway pressures and tidal volume were unchanged, airway obstruction was excluded and, with the strong suspicion of air embolism, the nitrous oxide was discontinued and manual ventilation of the lungs was performed with oxygen 100%. Within 2–3 min, the patient was placed supine. The PE'_{CO_2} increased to 4 kPa and the Sp_{O_2} increased to 100%. A catheter was inserted into the left radial artery and arterial blood gas analysis showed a Pa_{CO_2} of 5.4 kPa, while the PE'_{CO_2} was still 3.8 kPa. The surgery was stopped and the patient was awakened and his trachea extubated. He was conscious, haemodynamically stable and his Sp_{O_2} was 100% while breathing air. Neurological examination, biochemical and haematological

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

profiles, coagulation indices (indexed normalized ratio 1.12, thromboplastin time 30.12 s, D dimers 269 ng ml^{-1} and fibrinogen 412 mg ml^{-1}) and blood gas analysis were normal.

Seven hours after the presumed venous air embolism, the patient complained of nausea and retching. Metoclopramide 10 mg was administered i.m., with benefit. At that time, arterial blood gas analysis revealed mild hypoxaemia (Pa_{O_2} 9 kPa). Two hours later the patient suddenly complained of complete blindness, while his tendon reflexes were increased on the left side and a tremor was evident in the left arm. Ophthalmological examination revealed bilateral amaurosis without funduscopic abnormalities; the retinal vessels and the optic disc were normal. The patient underwent magnetic resonance imaging (MRI) including diffusion-weighted imaging (DW-MRI), which showed only a mild hyperintense area in the left cerebellar hemisphere with cortical–subcortical extension. Nevertheless, despite the negative MRI data, on the basis of a strong clinical suspicion of paradoxical air embolism the patient was transferred as rapidly as possible to a hyperbaric centre. It took 5 h from the onset of blindness to instigate hyperbaric therapy. During the first hyperbaric session (Table 1) the patient's sight started to recover (he could see shadows).

Table 1 Scheme of the early hyperbaric treatment

Gas mixture	Maximum pressure in atmospheres (ATA)	Time (h:min)
Oxygen in helium 50%	4	8:00
Oxygen 100%	2.8	0:25
Air	2.2	0:5
Air	1.8	0:5

Thirty hours later, a new MRI showed two hyperintense areas in the left cerebellar hemisphere with cortical–subcortical extension and bilateral hyperintensity in the cortical occipital gyrus, more evident on the right side than the left. A single-photon emission tomography (SPET) study of the brain was performed (Fig. 1), and this demonstrated a reduced uptake of isotopic tracer (99mTc-HMPAO, 740 MBq) in the right cerebellar hemisphere (Fig. 1A) and bilateral cerebral occipital (Fig. 1B) and left frontal (Fig. 1C) defects. Immediately after the SPET study, contrast transthoracic echocardiography was performed. No evidence of air in the right side of the heart or of interatrial

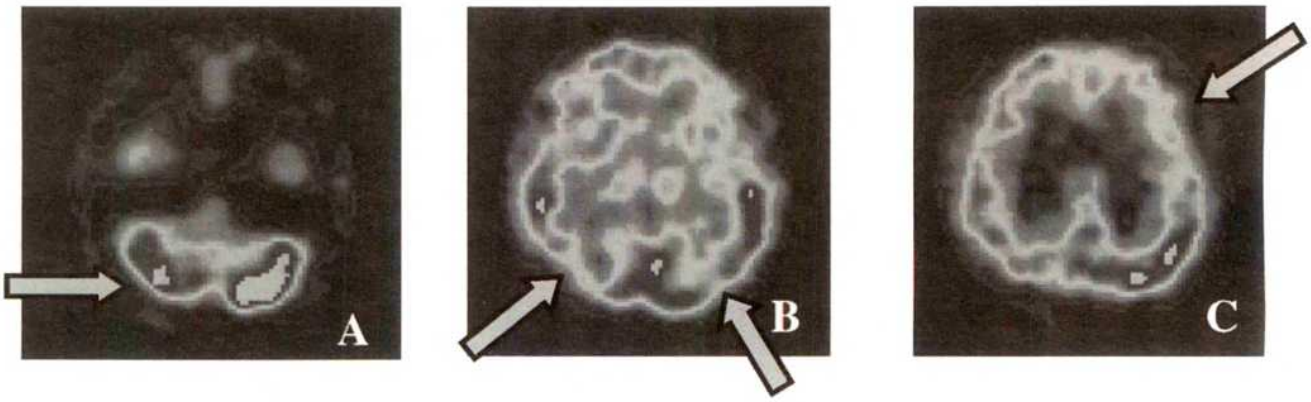


Fig 1 Three representative transverse slices of the SPET study of the brain with 99mTc-HMPAO, performed 31 h after paradoxical air embolism. (A) The arrow indicates a right cerebellar hemisphere uptake defect with interhemispheric asymmetry. (B) The arrow indicates bilateral occipital defects. (C) The arrow indicates a left frontal defect.

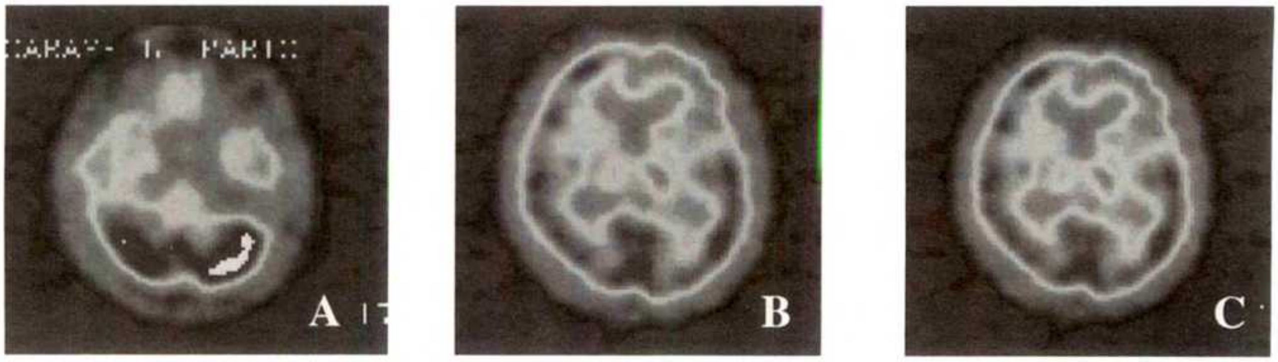


Fig 2 SPET study of the brain performed 13 days after injury. Mild interhemispheric cerebellar asymmetry (A) and completely normal tracer uptake in the occipital (B) and frontal (C) cerebral regions.

or interventricular shunt was found, even after a Valsalva manoeuvre. Hyperbaric therapy was scheduled daily for 9 days (1.8 bar for 80 min), even though the patient recovered completely about 48 h after the paradoxical air embolism. Thirteen days after surgery, a further SPET study provided evidence of complete recovery of the occipital (Fig. 2B) and frontal (Fig. 2C) defects, only a mild interhemispheric cerebellar asymmetry persisting (Fig. 2A).

Discussion

The phenomenon of pyelovenous backflow was first described in 1856 by Gigon, who noted the passage of fluids from the calyces into the renal veins.[1] Later, pyelovenous[2 3] and tubulovenous[4] backflow was described. Air embolism as a complication of retrograde pyelography[5] and air entering the hepatic veins after nephrolithotripsy have been reported.[6] Saline solution flowing from a bag placed 40 cm above the surgical field applies a pressure of about 4 kPa to the pelvocaliceal space. This pressure is reduced by an unknown amount by the aspirating pump. Because of the high rate of saline flow, accidental injection of small amounts of air, in the form of microbubbles, cannot be excluded. In addition, the high power of therapeutic shock waves could induce cavitation,[7] an ultrasound-related mechanical effect. The prone position[8] of the patient in this case produced a significant gravitational gradient between the right side of the heart and the renal pelvis, and air could thus have been drawn into open veins by negative pressure. This case demonstrates the problems associated with the combination of a gravitational gradient,[9] decreased caval pressure due to the position of the lower limbs, a likely high pressure[5] of irrigating fluid, possibly containing air bubbles,[10 11] and ultrasound shock waves.[12]

Air bubbles, the surfaces of which are covered by a network of fibrin, platelets and fat globules, induce neutrophil-mediated microvascular damage, activate the intrinsic coagulation cascade and obstruct lung capillaries. This will cause an increased physiological dead space,[13 14] disordered ventilation–perfusion matching[15] and reduced cardiac output as a result of right ventricular outflow obstruction, leading to decreased $P\text{E}'_{\text{CO}_2}$, $S\text{p}_{\text{O}_2}$ and systolic arterial pressure, together with an increased end-tidal arterial carbon dioxide gradient. In our case, we assumed venous air embolism rather than pulmonary thromboembolism, because coagulation was normal and there was a rapid improvement after ventilation with oxygen 100%. The oxygen concentration gradient could have facilitated the release from the air embolus of both nitrogen and nitrous oxide.

Eight hours after the venous air embolism, the patient displayed the features of the air having moved to the arterial side of the circulation, a phenomenon described most frequently in acute decompression illness after diving.

We used $P\text{E}'_{\text{CO}_2}$ to detect air embolism.[16] Doppler transthoracic ultrasound is more sensitive, but only early transoesophageal echocardiography might have demonstrated the presence of air which could progress through either a patent foramen ovale or through pulmonary shunts[16] to cause paradoxical air embolism. In our case, transoesophageal echocardiography did not demonstrate right-to-left interatrial shunting. However, the delay between venous and arterial embolic episodes suggests transpulmonary passage, which has been described in dogs[17] and humans[18] and has also been demonstrated by transoesophageal echocardiography.[19 20] Pathways involved in transatrial or transpulmonary air transport become functionally open only during episodes of venous air embolism in which significant elevation of pulmonary artery pressure occurs.[19] In our case, such an increase in pulmonary artery pressure could have been induced during the retching episodes. While the patient was in the head-up position, air crossing to the systemic arterial circulation could have migrated up to the carotid and cerebellar arteries and then to the cerebral and cerebellar hemispheres.[18]

Although DW-MRI is widely recognized to be the earliest imaging technique that detects brain ischaemia, in our case the early MRI scan (performed immediately after the onset of symptoms) did not show abnormalities consistent with ischaemic tissue, as described in a similar case report.[21] These findings could be related to the small dimensions of the injured areas[21] at the time of the first MRI scan. The later DW-MRI scan demonstrated abnormalities consistent with ischaemic brain damage in the occipital and cerebellar cortex. The SPET study of the brain confirmed these findings with enhanced sensitivity in indicating the extent and localization of the brain damage, even though the total number of counts recorded was only 9 000 000, with a reduced acquisition time (Fig. 1). The second SPET study (Fig. 2), which recorded a total of 13 000 000 counts with a standard acquisition time, provided definitive evidence of recovery.

In neurosurgical procedures in which the patient is in the sitting position, invasive monitoring to detect venous air embolism and the insertion of a catheter in the right atrium to aspirate air are used routinely. In other surgical procedures,[10] such as nephrolithotripsy, these precautionary measures may not be so easily justified. However, our case suggests that transoesophageal echocardiography can demonstrate the presence of air in the right heart or pulmonary veins, and this should be removed from the venous circulation through a right atrial catheter. In the case of persistent air trapping, prophylactic hyperbaric oxygen therapy should be performed. Until prospective studies provide an estimate of the true incidence of venous air embolism and paradoxical air embolism, it is difficult to decide whether transoesophageal echocardiography and central venous catheterization should be used routinely during percutaneous lithotripsy.

References

1 Lopez FA, Dalinka M, Doboy JG. Pyelovenous backflow in the human kidney. Facts, fallacies and significance. *Urology* 1973; **2**: 612–14

2 Hinman F, Lee-Braun RK. Pyelovenous backflow. *JAMA* 1924; **82**: 607–9

3 Olsson O. Studies on back-flow in excretion urography. *Acta Radiol* 1948; **29**: 3–6

4 Baghavan BS, Wenk RE, Dutta D. Pathways of urinary backflow in obstructive uropathy. *Hum Pathol* 1979; **10**: 669–83

5 Pyron CL, Segal AJ Air embolism: a potential complication of retrograde pyelography. *J Urol* 1983; **130**: 125–6

6 Miller RA, Kellett MJ, Wickham JE. Air embolism, a new complication of percutaneous nephrolithotomy. *J Urol (Paris)* 1984; **90**: 337–9

7 American Institute of Ultrasound Medicine. Mechanical bioeffects from diagnostic ultrasound. AIUM Consensus statements. *J Ultrasound Med* 2000; **19**: 69–168

8 Albin MS, Ritter RR, Pruett CE, Kalff K. Venous air embolism during lumbar laminectomy in the prone position: report of three cases. *Anesth Analg* 1991; **73**: 346–9

9 Albin MS, Ritter RR, Reinhart R, Erickson D, Rockwood A Venous air embolism during radical retropubic prostatectomy. *Anesth Analg* 1992; **74**· 151–3

10 Hofsess DW. Fatal air embolism during transurethral resection. *J Urol* 1984; **131**: 355

11 Vacanti CA, Lodhia KL. Fatal massive air embolism during transurethral resection of the prostate. *Anesthesiology* 1991; **74**: 186–7

12 Delius M, Enders G, Xuan Z, et *al*. Biological effects of shock waves: kidney damage by shock waves in dogs—dose dependence. *Ultrasound Med Biol* 1988; **14**: 117–22

13 Presson RG, Kirk KR, Hasselby KA, et *al*. Fate of air emboli in the pulmonary circulation. *J Appl Physiol* 1989; **67**: 1898–902

14 Albertine KH, Wiener-Kronish JP, Koike K, et *al* Quantification of damage by air emboli to lung microvessels in anesthetized dogs. *J Appl Physiol* 1984; **54**: 1360–8

15 Orebaugh SL. Venous air embolism: clinical and experimental considerations. *Crit Care Med* 1992; **20**· 1169–77

16 Chang J, Albin MS, Bunegin L, Hunt T. Analysis and comparison of venous air embolism detection methods. *Neurosurgery* 1980; **7**: 135–41

17 Buttler BD, Hills BA. Transpulmonary passage of venous air emboli. *J Appl Physiol* 1985; **59**: 543–7

18 Tommasino C, Rizzardi R, Beretta L, Venturino M, Piccoli S. Cerebral ischemia after venous embolism in the absence of cardiac defects. *J Neurosurg Anesth* 1996; **8**: 30–4

19 Bedell EA, Berge KH, Losasso TJ Paradoxic air embolism during venous embolism: transesophageal echocardographic evidence of transpulmonary air passage. *Anesthesiology* 1994; **80**: 947–50

20 Thrackeray NM, Murphy PM, McLean RF, DeLacy JL Venous air embolism accompanied by echocardiographic evidence of transpulmonary air passage. *Crit Care Med* 1996; **24**: 359–61

21 Sayama T, Mitani M, Inamura T, Yagi H, Fukui M. Normal diffusion weighted imaging in cerebral air embolism complicating angiography. *Neuroradiology* 2000; **42**: 192–4

British Journal of Anaesthesia 89 (5): 778–82 (2002)

Epidural abscess complicating insertion of epidural catheters

J. M. G. Phillips[1], J. C. Stedeford[2], E. Hartsilver and C. Roberts*

Gloucestershire Royal Hospital, Great Western Road, Gloucester GL1 3NN, UK

[1]Present address: Musgrove Park Hospital, Taunton, Somerset, UK

[2]Present address: Bristol Royal Infirmary, Bristol, UK

[3]Present address: Royal Devon and Exeter Hospital, Exeter, UK

**Corresponding author*

We present three cases of epidural abscess, all in patients in whom an epidural catheter had been inserted for postoperative pain management. In all three cases the infecting organism was *Staphylococcus aureus* and two patients had diabetes. The diagnosis was made within 3 days of epidural catheter removal in two cases, but in one the abscess did not present until after the patient had been discharged from hospital. We have retrospectively calculated the incidence of epidural abscess in our hospital over the 5-yr period 1993–98 to be 1 in 800 (0.12%). We emphasize the importance of using techniques that minimize the risk of bacterial contamination during both catheter placement and the management of infusion, and seek to raise awareness of this relatively rare but significant condition.

Br J Anaesth 2002; **89**: 778–82

Keywords: anaesthesia; epidural; complications, epidural abscess

Accepted for publication: May 30, 2002

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Epidural abscess is a rare but serious complication of epidural catheter insertion.[1] The incidence of this condition is unclear. The first case of catheter-related epidural abscess was described in 1974 and a further 41 cases were reported up to 1996.[2] We report three case reports from our hospital and discuss the aetiological factors, clinical presentation, management and consequences of this condition.

Case reports

Patient 1

A 75-yr-old woman with carcinoma of the caecum was admitted for a right hemicolectomy. Her medical history was unremarkable. Before induction of anaesthesia a thoracic epidural catheter was sited aseptically. The anaesthetist wore a cap, sterile gloves and a gown; the skin was prepared with 10% iodine and the catheter was dressed with a sterile occlusive dressing. Subcutaneous heparin and i.v. gentamicin and metronidazole were administered in the anaesthetic room. A continuous epidural infusion of bupivacaine and diamorphine was administered for postoperative analgesia. After 3 days the epidural catheter was removed intact.

Over the next day the patient developed a low-grade pyrexia with no obvious cause. This persisted until the fifth day after surgery, when she also spiked a temperature. At this stage she complained of low backache and a headache. There was local tenderness over the epidural site but no neurological deficit or meningism. C-reactive protein (CRP) concentration was 126 mg litre^{-1} and the white cell count (WCC) was 9.6×10^9 litre^{-1} with a neutrophil count of 8.2×10^9 litre^{-1}. A possible diagnosis of epidural abscess was considered. Swabs were taken from the epidural site and i.v. flucloxacillin and cefuroxime were started. The patient's condition improved over the next few days. *Staphylococcus aureus* sensitive to flucloxacillin was cultured from the epidural site specimen. Sixteen days after the operation the patient was apyrexial but complained of persistent lower back pain. Magnetic resonance imaging (MRI) showed a focus of enhancement in the posterior epidural space. This pattern is usually associated with granulation tissue and inflamed fat rather than pus. However, the patient had been on i.v. antibiotics for several days. She was referred to the neurosurgeons, who treated the condition conservatively with i.v. flucloxacillin and fucidin, since there were no signs of cord compression. Forty-four days after surgery she was discharged home on a further 2-week course of oral antibiotics. A follow-up MRI scan showed resolution of the initial findings.

Patient 2

A 55-yr-old man was admitted for an above-knee amputation. He had a medical history of peripheral vascular disease, hypertension, ischaemic heart disease, insulin-dependent diabetes mellitus and a resolved cerebrovascular accident.

Anaesthesia was provided by a combined lumbar spinal and epidural technique. This was performed using the aseptic technique described above. A continuous infusion of bupivacaine and diamorphine provided postoperative analgesia for 3 days, after which the epidural catheter was removed intact.

Three days after removal of the catheter, the patient reported discomfort at the epidural insertion site and a severe radicular pain in the distribution of the L2 dermatome. He had a mild pyrexia of 37.2°C and an erythematous tender swelling at the epidural insertion site. Neurological examination revealed loss of sensation to pin prick and light touch in the remaining leg, together with decreased power and an absent right ankle reflex. Blood tests showed a CRP of 118 mg litre^{-1} and a WCC of 13.9×10^9 litre^{-1}. An MRI scan showed a right posterolateral epidural abscess at L1/2 causing slight thecal displacement. The patient was urgently referred for neurosurgical review and underwent laminectomy and drainage of an epidural abscess. Swabs taken at the time of operation cultured *S. aureus* sensitive to flucloxacillin, which had been started at the time of operation. He was discharged from hospital 3 months after his first operation.

Patient 3

A 63-yr-old man presented for emergency surgery with a leaking abdominal aortic aneurysm (AAA). He had a history of diet-controlled diabetes and a recent chest infection. He underwent an emergency AAA repair. After induction of anaesthesia he was given augmentin 1.2 g i.v. He received three further doses over the next 24 h as prophylaxis against graft infection. He was initially transferred to the intensive care unit (ITU) where, on the first day after surgery, when his coagulation profile was within normal limits, a thoracic epidural catheter was inserted under aseptic conditions and a continuous infusion of bupivacaine and diamorphine was started.

The patient was transferred to the high-dependency unit on the second day after surgery. On the fourth day the epidural catheter was removed intact and the patient was discharged home 1 week after admission, having made a straightforward recovery.

Three weeks later the patient was re-admitted with a 5–6 day history of infection over the epidural site, which had been treated by his general practitioner with oral flucloxacillin. He had developed pain over the epidural site 4 days before re-admission, and on the day of re-admission he had developed sudden and progressive weakness in his legs and urinary retention. At this time he had no evidence of superficial infection at the epidural insertion site. He was apyrexial and had a white cell count of 8.2×10^9 litre^{-1}. An urgent epidural myelogram showed an epidural collection causing extradural cord compression at T8. A sample of cerebrospinal fluid sent for culture at that time yielded no bacterial growth. Peripheral blood cultures were also negative. The patient was transferred to a neurosurgical unit where a T6–8 laminectomy was performed. Culture of abscess material grew methicillin-resistant *S. aureus* (MRSA) and the patient was treated with teicoplanin. The power in his legs returned such that he was able to walk around the ward. Seven days after surgery he suffered a cardiac arrest from which he could not be resuscitated. Postmortem examination established the cause of death to be a pulmonary embolus secondary to a deep vein thrombosis.

Nose, throat and skin swabs taken by the anaesthetist who inserted the epidural catheter did not grow MRSA. However, the strain of MRSA cultured from samples taken from the epidural abscess during laminectomy was also isolated from swabs taken from another patient who had been on the same ward as our patient after discharge from the ITU. This MRSA strain was not cultured from any of the routine swabs taken from patients on the ITU during the patient's stay. We therefore presume that the infection could have been acquired at some point following transfer to the general ward.

Discussion

Epidural abscess is a rare condition, with a reported incidence of 1–2/10 000 of all patients admitted to hospital.[3 4] The incidence in association with epidural catheter placement *per se* is unclear. The published data quote frequencies ranging from 1 in 506 000 cases, reported in a retrospective review of obstetric patients who underwent epidural anaesthesia for vaginal delivery or Caesarean section,[5] to 3% in patients who had epidural catheters inserted for chronic pain indications.[6] The latter study described two epidural abscesses in only 60 cases of catheter insertion and thus is unlikely to be an accurate statistical analysis of the true occurrence rate. A recent study of epidural catheters inserted over a 1-yr period in Denmark revealed an abscess rate of 1 in 1930 (0.05%).[7] This aimed to include epidural catheters inserted for all indications in all anaesthetic departments in the country.

In our retrospective review of 2401 patients who received epidural postoperative analgesia over a 5-yr period the incidence of epidural abscess was 0.125%. However, this does not include epidural catheters inserted for obstetric indications, which over the same time period amounted to a further 5000 cases, without a single case of epidural abscess. If these cases are included, the incidence falls to 0.04%.

Infection of the epidural space may occur at the time of insertion of the epidural catheter[8] or by subsequent contamination by one of three different ways:[9] through contamination of the skin site and subsequent spread along the catheter track, by haematological spread, or by intraluminar contamination via a contaminated syringe[10] or contaminated local anaesthetic solution.[11]

Infection at the time of insertion has been implicated in one published case in which the infecting organism was later isolated from nasal swabs taken from the anaesthetist.[8] There are factors that the anaesthetist can control to reduce the risk of contamination during insertion. These include the use of a strict aseptic technique and the choice of skin dressing used to secure the epidural catheter.

We believe that strict aseptic technique during catheter insertion should include wearing sterile gloves and gown, a theatre cap and a facemask. The skin should be prepared with a suitable bactericidal agent, allowing time to ensure effective antibacterial action. *In vitro* studies have shown that exposing a suspension of MRSA and methicillin-susceptible *S. aureus* to 10% povidone iodine for either 15 or 60 s will result in a 55.2% and 96.7% reduction in mean colony count, respectively.[12] Furthermore, no organism was cultured after the same suspension was exposed to 0.5% chlorhexidine in 80% ethanol for 15 s.

In all three patients described above, 10% povidone iodine was used for skin preparation. However, there was no record of how long it was allowed to dry. At this time it was not policy to use chlorhexidine routinely. Infection during insertion is unlikely to have occurred in patient 3, since swabs taken from the anaesthetist did not grow MRSA. The same strain of MRSA cultured from the abscess fluid was, however, also cultured from a patient who was on the same ward as patient 3 after discharge from the ITU. At this stage the epidural catheter had been *in situ* for 24 h.

Skin colonization by bacteria at the site of the epidural catheter puncture may occur at the time of placement or later. One study has shown that even when aseptic techniques are used, the epidural and spinal needles can become contaminated with a variety of organisms which may introduce pathogens into the epidural space and lead to clinical infection.[13] The type of dressing used to secure the catheter may influence infection as a result of skin contamination. The use of a porous dressing might be less likely to encourage bacterial culture by reducing the potential for fluid accumulation, but might increase the possibility of secondary pathogen colonization by the passage of bacteria through the dressing. This could have occurred in patient 3.

Contamination of the epidural infusate is a further possible mechanism of infection. In all three patients a continuous infusion of bupivacaine and diamorphine was established after insertion of the epidural catheter. A closed delivery system and bacterial filter were used, in line with published recommendations.[14] The infusate was delivered through a 60-ml syringe prepared by the anaesthetist. We have now changed to using 250-ml bags of 0.15% bupivacaine with diamorphine prepared in the pharmacy under sterile conditions. This may reduce the likelihood of contamination during preparation and during syringe changes.[15] A recently published analysis of factors associated with epidural infection reported an increased risk of infection when the epidural infusate is administered via a 60-ml syringe driver rather than an infusion bag.[16] It is interesting to note that mixtures of bupivacaine and diamorphine in concentrations used clinically have bactericidal activity against commonly encountered skin organisms.[17]

Attention to asepsis is important throughout the period the catheter is *in situ* as infection can occur whilst the patient is on the ward. The most common organism cultured from epidural abscesses is *S. aureus*,[11] which we found in all three of our patients. Epidural abscess due to MRSA, as in patient 3, has been previously described in only one case in the literature.[18] Other organisms less commonly implicated are gram-negative bacilli, anaerobic bacteria and mycobacteria.[3 4 14 15] MRSA is a growing problem in hospitals. Each hospital should have policies in place regarding admission to wards known to have MRSA-colonized or -infected patients. Whether these wards are closed to admission of patients, particularly those more susceptible to infection, depends on a number of factors, such as the strain of MRSA, number of cases and availability of alternative facilities.[19]

Infection of the epidural space is more likely to occur in certain patient groups. Patients 2 and 3 both had diabetes mellitus. Association of epidural infection with diabetes mellitus has been shown to be strong, one study showing that 13% of patients presenting with epidural abscesses without prior spinal injections also had diabetes mellitus.[3] With epidural anaesthesia, identifiable risk factors other than diabetes mellitus are chronic renal failure, cancer, steroid administration, herpes zoster and rheumatoid arthritis.[11]

Patients 1 and 2 both received intraoperative antibiotics; however, whilst providing good surgical prophylaxis, these antibiotics are unlikely to have good bactericidial action against *S. aureus*. Antibiotics are not given to cover epidural catheter insertion and there is no evidence to support their introduction. Given the low incidence of epidural abscess, it would be very difficult to show a positive effect of prophylactic antibiotics.

The common presenting symptoms of epidural abscess are backache (72%), radicular pain (47%), weakness of an extremity (35%), sensory deficit (23%), bladder or bowel dysfunction (30%), and paralysis (21%).[20] Presentation may, however, be variable and pyrexia is not always present.[21 22] All three of our patients had backache but only two had a fever at the time of diagnosis. The third patient had been treated for a period with oral antibiotics before hospital admission, which may have masked the fever. If the symptoms do suggest a diagnosis of epidural abscess, then an MRI scan is the investigation of choice and eliminates the need for dural puncture.[23 24]

The successful management of epidural abscess relies on an early dignosis and surgical decompression and debridement, followed by antibiotics.[4 22 25] A non-surgical approach to management has been described.[26 27] Patients 2 and 3 were managed surgically and patient 1 conservatively. In patient 2, diagnosis was prompt after the onset of symptoms. In patient 1, a definitive diagnosis was delayed until MRI scans were performed, although the patient was treated with i.v. antibiotics at an early stage for a presumptive abscess. An earlier MRI scan and referral to the neurosurgical centre would have been appropriate. Patient 3's diagnosis was delayed until the onset of a profound neurological deficit. This was despite the presence of local infection over the epidural site and the onset of lower back pain. The onset of symptoms and signs occurred in the primary setting and it is thus important to raise awareness amongst general practitioners of the possibility of such problems, especially as epidural anaesthesia is becoming increasingly popular, and postoperative discharge from hospital to the care of the general practitioner is occurring earlier.

Whilst the benefits of epidural catheters in the management of postoperative pain have been widely documented, the accompanying risks must not be forgotten. Apart from epidural abscess formation, other complications with serious consequences, such as epidural haematomas and nerve damage, may also occur. These complications are also rare. Epidural abscesses occur at a cost both to the patient and the hospital. A patient with an epidural abscess will have a prolonged stay in hospital, may undergo a spinal decompression and may be left with a permanent neurological deficit. The recovery rate from epidural abscess is poor. One survey of patients who received surgical intervention for epidural abscess revealed that of the seven patients who were paralysed before surgery, five died and two were paralysed permanently. Of the eleven patients who had only some neurological deficit, only three made a full recovery.[28]

Hospital costs are also considerable. The patient may stay in hospital for several weeks, requiring full nursing care. Patient 1 stayed in hospital for 6 weeks and patient 3 for 3 months. Diagnosis requires MRI scanning, which may not be readily available. Treatment may also involve transfer to a neurosurgical centre and the cost of a spinal decompression.

Since the occurrence of these three cases we have reviewed our practice and have re-emphasized that the following guidelines are adhered to. Epidurals should be inserted in a clean area (anaesthetic room or theatre). The anaesthetist should observe a strict aseptic technique, washing their hands with chlorhexidine for 2 min and wearing a theatre cap, facemask, sterile gloves and gown. The skin should be prepared with 0.5% chlorhexidine in 80% ethanol and this should be left for 2 min before attempting epidural insertion. A sterile drape is placed around the insertion site. After catheter insertion, a semipermeable occlusive dressing (Opsite 3000) is applied. The dressing is inspected daily by the acute pain sister and is only changed if the catheter is to remain in place for longer than 3 days or if there is any blood staining. Infusates are prepared in 250-ml bags under sterile conditions in the pharmacy. We thus aim to minimize the chances of contamination by processes under the control of the clinician and acute pain team. In addition, we have raised the profile of epidural abscess as a complication of epidural analgesia amongst both hospital staff and general practitioners in order to ensure early diagnosis and appropriate investigation and treatment.

Acknowledgements

We wish to thank Dr RG Vanner (consultant anaesthetist) and Dr E Brown (consultant radiologist) for their help in preparing the manuscript.

References

1 Chadwick HS, Bonica JJ. Complications of regional anaesthesia. In: Bonica JJ McDonald JS, eds *Principles and Practice of Obstetric Analgesia and Anaesthesia* 2nd Edn. Baltimore: Williams & Wilkins, 1995; 538–72

2 Kindler CH, Seeberger MD, Staender SE. Epidural abscess complicating epidural anesthesia and analgesia. *Acta Anaesthesiol Scand* 1998; **42:** 614–20

3 Baker AS, Ojemann RG, Swartz MN, Richardson EP Jr. Spinal epidural abscess. *N Engl J Med* 1975, **293:** 463–8

4 Hlavin ML, Kaminski HJ, Ross JS, Ganz E. Spinal epidural abscess: a ten year perspective. *Neurosurgery* 1990; **27:** 177–84

5 Scott DB, Hibbard BM. Serious non-fatal complications associated with epidural block in obstetric practice. *Br J Anaesth* 1990, **64:** 537–41

6 Strong WE Epidural abscess associated with epidural catheterisation: A rare event? Report of two cases with markedly delayed presentation. *Anesthesiology* 1991; **74:** 943–6

7 Wang LP, Hauerberg J, Schmidt JF. Incidence of spinal epidural abscess after epidural analgesia. A national 1-year survey. *Anesthesiology* 1999; **91:** 928–36

8 North JB, Brophy BP. Epidural abscess; a hazard of spinal epidural anaesthesia. *Aust N Z J Surg* 1979; **49:** 484–5

9 Holt HM, Anderson SS, Anderson O, Gahrn-Hansen B, Siboni K. Infections following epidural catheterisation. *J Hosp Infect* 1995; **30:** 253–60

10 James FM, George RH, Naiem H, White GJ. Bacteriological aspects of epidural analgesia. *Anesth Analg* 1976; **55:** 187–90

11 NganKee WD, Jones MR, Thomas P, Worth RJ. Extradural abscess complicating extradural anaesthesia for caesarean section. *Br J Anaesth* 1992, **69:** 647–52

12 Sakurgi T, Yanagisawa K, Dan K. Bactericidal activity of skin disinfectants on methicillin-resistant *Staphylococcus aureus*. *Anesth Analg* 1995; **81:** 555–8

13 Radler C, Lass-Flori C, Puhringer F, Kolbitsch Ch, Lingnau W, Benzer A. Bacterial contamination of needles used for spinal and epidural anaesthelsa. *Br J Anaesth* 1999; **83:** 657–8

14 Scott DB, Walker LR. Administration of continuous epidural analgesia. *Anaesthesia* 1963; **18:** 82–3

15 Dawson P, Rosenfeld JV, Murphy MA, Hellyar AG. Epidural abscess associated with postoperative epidural analgesia. *Anaesth Intens Care* 1991; **19:** 569–91

16 Dawson SJ, Small H, Logan MN, Geringer S. Case control study of epidural catheter infections in a district general hospital *Commun Dis Public Health* 2000; **3:** 300–2

17 Cook TM, James PA, Stannard CF. Diamorphine and bupivacaine mixtures: an in vitro study of microbiological safety. *Pain* 1998; **76:** 259–63

18 Yuste M, Canet J, Garcia M, Gil MA, Vidal F. An epidural abscess due to resistant Staphylococcus aureus following epidural catheterisation. *Anaesthesia* 1997; **52:** 150–68

19 WorkingParty Report. Revised guidelines for the control of methicillin-resistant *Staphylococcus aureus* infection in hospitals. *J Hosp Inf* 1998; **39:** 253–90

20 Darouiche RO, Hamill RJ, Greenberg SB, Weathers SW, Musher DM. Bacterial spinal epidural abscess. Review of 43 cases and literature survey. *Medicine* 1992; **71:** 369–85

21 Curling OD Jr, Gower DJ, McWorter JM. Changing concepts in spinal epidural abscess. A report of 29 cases. *Neurosurgery* 1990; **27:** 185–92

22 Danner RL, Hartmann BJ. Update of spinal epidural abscess; 35 cases and review of the literature *Rev Infect Dis* 1987;**9:** 265–74

23 Maslen DR, Jones SR, Crislip MA, Bracis R, Dworkin RJ, Flemming JE. Spinal epidural abscess. Optimising patient care. *Arch Intern Med* 1993; **153:** 1713–21

24 Erntell M, Holtas S, Norlin K, Dalhlquist E, Nilsson-Ehle I. Magnetic resonance imaging in the diagnosis of spinal epidural abscess. *Scand J Infect Dis* 1988; **20:** 323–7

25 Heusner AP. Non-tuberculous spinal epidural infections. *N Engl J Med* 1948; **239:** 845–54

26 Dysart RH, Balakrishnan V. Conservative management of extradural abscess complicating spinal extradural anaesthesia for caesarian section. *Br J Anaesth* 1997; **78:** 591–3

27 Bengtsson M, Nettelbland H, Sjoberg F. Extradural catheter-related infections in patients with infected cutaneous wounds. *Br J Anaesth* 1997; **79:** 668–70

28 Hlavin ML, Kaminski HJ, Ross JS, Ganz E. Spinal epidural abcess: a ten-year perspective. *Neurosurgery* 1990; **27:** 177–84

British Journal of Anaesthesia 89 (5) 782–5 (2002)

Unexplained fitting in three parturients suffering from postdural puncture headache

C. D. Oliver[1 2]* and S. A. White[1 3]

[1]*Whipps Cross Hospital, Whipps Cross Road, Leytonstone, London E11 1NR, UK*

[2]*Present address: Department of Anaesthetics, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK.* [3]*Present address: Department of Anaesthetics, Royal London Hospital, Whitechapel, London E1 1BB, UK*

**Corresponding author*

We present the cases of three women who, within a 6-month period, suffered post-partum generalized tonic–clonic seizures. All had received an epidural in labour for analgesia and were

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

subsequently diagnosed as suffering from postdural puncture headache. All were treated for that headache with Synacthen and one also received sumatriptan before her seizures. All made satisfactory recoveries and were discharged home. None displayed classical patterns suggestive of pre-eclampsia, meningitis, cortical venous thrombosis or any other pathological process that might explain these events adequately, and the specific precipitating factors were left unidentified.

Br J Anaesth 2002; **89**: 782–5

Key words: anaesthesia, obstetric; complications, convulsions; complications, postdural puncture headache; pharmacology, sumatriptan; pharmacology, Synacthen

Accepted for publication: June 17, 2002

Case 1

A previously fit 37-yr-old primiparous woman with an uneventful pregnancy received epidural analgesia during labour. The hospital notes recorded the epidural procedure as 'difficult' but gave no specific details. Uterine contractions were augmented with Syntocinon and the woman had a normal vaginal delivery.

She complained of a headache immediately after delivery and was given acetaminophen with initial good effect. However, the headache returned the following day and was treated with co-proxamol. The headache persisted, becoming progressively more severe and positional, and radiating to the neck. It was then diagnosed as a postdural puncture headache (PDPH). A previous history of migraine effectively treated with sumatriptan was also elicited at this time and she was treated with bed rest, i.v. fluids and sumatriptan 100 mg orally, which resulted in resolution of her symptoms.

She again complained of headache on day 2 after delivery and was given a further dose of sumatriptan, which once again provided good relief. However, the headache recurred and was further treated with compound analgesics and oral fluids.

On day 4, despite analgesics, the headache continued and so she was given i.m. Synacthen 1 mg, and i.v. fluids were recommenced. A blood patch was discussed at this stage. Later that day the headache worsened and she vomited repeatedly. She was given morphine i.m., which relieved the headache, and the vomiting settled with metoclopramide. Her white cell count (WCC) at this time was 10.8×10^9 litre^{-1}.

By day 6, her headache had not resolved and a further dose of Synacthen 1 mg i.m. was given, followed by another dose of sumatriptan 100 mg orally. Until this point in the postpartum period, there had been no abnormal neurological signs and no evidence of hypertension. Then she suffered two short-lived grand mal seizures, which were treated with diazepam 5 mg and then 10 mg i.v. A loading dose of phenytoin was given and she was sedated, intubated, ventilated and transferred to the intensive care unit, where she was noted to have an arterial pressure of 170/100 mm Hg.

The arterial pressure remained elevated for several hours after fitting, and was treated with sublingual nifedipine. She was extubated on day 7. A computed tomography (CT) scan of her head later that day revealed a low-attenuation area in the right occipitoparietal lobe and a smaller area in the left posterior parietal lobe, both suggestive of infarction. A subsequent lumbar puncture was normal. At this time she had no focal neurology, was afebrile and blood urea and electrolytes were normal. The WCC was 15×10^9 litre^{-1}.

She was commenced on carbamazepine with the intention of continuing it for a period of 6 months. She made an uneventful recovery, with no neurological deficit (despite the CT findings) before discharge on day 14.

Case 2

A 21-yr-old primiparous woman presented at her local hospital in labour at 39 weeks gestation, having previously been booked at another hospital, where antenatal attendance had been poor. She was generally healthy, suffering only from mild asthma (for which she used a salbutamol inhaler as required), and smoked 20–30 cigarettes per day. During her labour, an epidural was sited uneventfully before she underwent artificial rupture of membranes (ARM) and Syntocinon augmentation. She proceeded to normal vaginal delivery.

On day 1 after delivery she complained of neck pain with headache and a diagnosis of PDPH was made. Oral and i.v. hydration, compound oral analgesics (co-proxamol) and bed rest were prescribed. The possibility of a blood patch was discussed, but she expressed reservations. Because her headache persisted and was 'making hearing difficult', she was given Synacthen 1 mg i.m. Her arterial pressure at this time was 120/60 mm Hg and she was afebrile.

On day 2, she was still complaining of difficulty hearing and was feeling very sleepy. Despite this, she refused to comply with advice to remain in bed. Oral analgesia was changed to codeine and she received a second dose of

Synacthen 1 mg i.m. Her arterial pressure and temperature remained normal.

On day 3, although she was still sleepy, her headache was improving, resulting in her refusal of a third dose of Synacthen. On day 4, she refused all analgesics and was generally uncooperative despite the persistent headache. On day 5, she suffered a generalized tonic–clonic seizure, during which she became cyanosed. The fit resolved spontaneously and, although post-ictal, she was responding to command, moving all four limbs, her pupils were equal and reactive and she did not have papilloedema. Observations immediately after the seizure revealed an arterial pressure of 120/60 mm Hg and a heart rate of 100 beats min^{-1}. Blood tests revealed that blood sugar was 4.1 mmol $litre^{-1}$, WCC 16.8×10^9 $litre^{-1}$ and uric acid 0.31 mmol $litre^{-1}$. Urea and electrolytes, liver function tests and full blood count were all normal. Midstream urine, sputum and blood culture samples taken at this time were all later reported as negative for bacterial growth.

A second fit, 1 h later, was treated with diazepam 10 mg i.v. She was then intubated and ventilated and a CT head scan was performed. The scan showed small ventricles and meningeal hyperaemia. In the intensive care unit she was treated with phenytoin, cefotaxime and benzylpenicillin and was extubated later that day.

On day 6 she returned to the labour ward after having had a magnetic resonance imaging scan (MRI) of her brain, which was reported as normal. She self-discharged on day 12, still complaining of headache, and was lost to follow-up.

Case 3

This previously fit and well 33-yr-old primiparous lady also had an uneventful pregnancy. She was induced with Prostin vaginal pessaries and then ARM at term plus 13 days and sustained a dural tap on insertion of an epidural in labour. She underwent lower segment Caesarean section (LSCS) under general anaesthesia for failure to progress.

On day 1, she complained of frontal head and neck ache on sitting up and was diagnosed as having a PDPH. She had no neurological symptoms or signs at this time and was afebrile. She was treated with oral compound analgesics and i.v. fluid, and blood patch treatment was discussed.

On day 2, she still complained of headache, which was relieved by lying flat and taking regular oral analgesics. She was given Synacthen 1 mg i.m. but continued to complain of headache the following day and so was given a second dose of Synacthen 1 mg i.m. She was then encouraged to mobilize and i.v. fluids were discontinued.

She was given a third dose of Synacthen 1 mg i.m. on day 4, but by day 6 she was complaining of spots in front of her eyes, blurred vision and headache. She suffered a grand mal fit and became peripherally cyanosed (arterial pressure 170/100 mm Hg), but recovered spontaneously with facemask oxygen. After resolution of the fit, her arterial pressure was 126/71 mm Hg, pulse 80 beats min^{-1}, arterial oxygen saturation 95% and temperature normal. She was catheterized, i.v. access was established and i.v. hydration was resumed, but she was also allowed oral fluids.

At this time the midwife noted that the patient had a swollen face and feet, but neurological examination proved unremarkable. Clotting screen, urea and electrolytes, liver function tests and full blood count were all normal, uric acid was 0.45 mmol $litre^{-1}$ and there was only a trace of protein in her urine. Later the same day, she again complained of headache and, as her arterial pressure was recorded as 163/102 mm Hg, she was given nifedipine 10 mg orally. She had a non-contrast CT brain scan which was reported as normal. A loading dose of phenytoin was given, followed by maintenance therapy of 300 mg per day.

On day 7 her arterial pressure was still elevated, at 153/100 mm Hg, and an MRI of her brain was reported as showing a small infarct near the left trigone (near the posterior horn of the left lateral ventricle) and small focal ischaemic areas in the white matter. She was prescribed oral aspirin 75 mg daily and enoxaparin 40 mg s.c. Phenytoin was subsequently discontinued gradually and she made an uneventful recovery.

Discussion

The differential diagnosis of post-partum seizures includes: epilepsy; drug/alcohol withdrawal; pre-eclamptic toxaemia (PET); meningitis; space-occupying lesion; cerebral venous thrombosis (CVT); metabolic disturbance, (e.g. calcium and glucose); thrombotic thrombocytopaenic purpura (TTP); PDPH and certain treatments for PDPH, such as caffeine, sodium benzoate and sumatriptan. Investigation of the condition should include: arterial pressure and temperature measurement; urine and blood cultures; full blood count; urea and electrolytes; bone minerals; glucose; clotting; bleeding time; fibrinogen; liver function tests and erythrocyte sedimentation rate; EEG; CT head; lumbar puncture (if not contraindicated) and MRI to exclude CVT if appropriate.

None of the three ladies had a history of alcohol or drug abuse or of epilepsy. TTP and metabolic disturbance were excluded in all three by laboratory blood analysis. CT scanning failed to show potentially causal space-occupying lesions. None of the three women had any of the fluctuating motor or sensory focal neurological signs that are normally associated with CVT and two of the three had normal MRI scans. No convincing evidence of meningitis or PET was found, with only transitory post-ictal arterial pressure rises seen in two of the women.

After dural puncture, the continued loss of cerebrospinal fluid (CSF) leads to decreased volume and pressure of the CSF compartment.[1] This can cause a downward pulling or stretching of the intracranial contents as a result of the negative spinal–cranial pressure gradient. Cranial nerves, vessels, dura and brain parenchyma may be injured by stretching, leading to complications such as sixth nerve palsy, seizures,[2] subdural haematoma[3 4] and, very rarely, subarachnoid haemorrhage.[5] Decreased CSF pressure creates an abnormal pressure gradient between the cerebral vasculature and the CSF. As veins are thin-walled and, within certain limits, will adjust passively to pressures in and around them, it is likely that negative pressure on the outside of the vein wall will result in vasodilatation.[6] In addition, a sudden decrease in CSF volume is proposed to further propagate vasodilatation via activation of vascular adenosine receptors.[6 7]

Although PDPH is often self-limiting or resolves within 24 h of conservative treatment, such as analgesics and fluid therapy, the potential significant complications of the condition lead us to treat it more aggressively after this period. Reversal of the postdural puncture cerebral vasodilatation with vasoconstrictors has been tried with both caffeine and sumatriptan. Sumatriptan is a vasoconstrictor of pathologically dilated arterial vessels[8–10] and its actions may be dose-dependent and show regional variations. Its use is cautioned in pregnancy and breast-feeding.[11] Seizures have been reported with the use of both sumatriptan and i.v. caffeine.[12 13]

In pre-eclampsia, women have a relatively dehydrated intravascular circulation and a vasoconstricted cerebral vasculature.[10 14] PET can present post-partum and is seen as a spectrum of clinical disease. Post-partum eclamptic fits lead to cerebral vasospasm, ischaemia and infarction.[15] In women with both PET and PDPH, the use of vasoconstrictors to treat the PDPH would seem unwise. Indeed, there may be a group of women with subclinical PET who would be at increased risk of cerebral infarcts if their PDPH were treated with vasoconstrictors.

The mode of action of Synacthen in the treatment of PDPH is unknown.[16–18] It was given in this hospital for many years before recent requirements for audit and evidence-based medicine and thus no evaluation of its use as a treatment in this centre exists. Indeed, it was discontinued as a therapy for PDPH shortly after these three cases occurred. There are no published large-number trials in which the efficacy and side-effect profile of this treatment for PDPH have been fully evaluated. To date there are no reports in the literature of patients suffering seizures secondary to Synacthen therapy.

Currently, the most widely used treatment for unresolving PDPH is an aseptically performed epidural blood patch. However, recurrent headache is a common event unless the blood patch is delayed by at least 48 h, and the influence of the volume of blood injected is unclear.[19]

In these cases, it seems likely that the Synacthen was ineffective and the seizures were caused by the complications of untreated dural puncture. Further evaluation of the efficacy of Synacthen is needed before its use in the treatment of PDPH. Also, further evaluation of the effects of cerebral vasoconstrictors in the treatment of PDPH, particularly in women with PET, is needed before they are used routinely. Indeed, one of these three women may have suffered seizures as a result of sumatriptan therapy.

References

1 Olsen KS. Epidural blood patch in the treatment of post-lumbar puncture headache. *Pain* 1997; **30**: 293–301

2 Shearer VE, Jhaveri HS, Cunningham FG. Puerperal seizures after postdural puncture headache. *Am J Obstet Gynecol* 1995; **85**: 255–60

3 Fishman RA. *Cerebrospinal Fluid in Diseases of the Nervous System.* Philadelphia: W. B Saunders, 1992; 171–2

4 Reynolds F. Dural puncture and headache. *Br Med J* 1993, **306**: 874–5.

5 Bottinger BW, Diezel G. Akute intrakranielle Subarachnoidalblutung nach wiederholter Spinalanasthesie. *Anaesthesist* 1991; **41**: 152–7

6 Fernandez E. Headaches associated with low spinal fluid pressure *Headache* 1990; **30**: 122–8

7 Raskin NH. Lumbar puncture headache: a review. *Headache* 1990; **30**: 197–200

8 Schmetterer L, Woltz M, Krejcy K, *et al.* Cerebral and ocular hemodynamic effects of sumatriptan in the nitroglycerin headache model. *Clin Pharmacol Ther* 1996; **60**: 199–205

9 Nilsson F, Nilsson T, Edvinsson L, *et al.* Sumatriptan-induced vasoconstriction as treatment of experimental intracranial hypertension. *Acta Anaesthesiol Scand* 1996; **40**: 612–20

10 Lewis LK, Hinshaw DB, Will AD, Hasso AN, Thompson JR. CT and angiographic correlation of severe neurological disease in toxaemia of pregnancy. *Neuroradiology* 1988; **30**: 59–64.

11 *British National Formulary.* BMA Publications, 2001; **41**: 220, 222

12 Cohen SM, Laurito CE, Curran MJ. Grand mal seizure in a postpartum patient following infusion of caffeine sodium benzoate to treat persistent headache. *J Clin Anesth* 1992; **4**: 48–51.

13 Frison LM, Dorsey DL. Epidural blood patch and late postpartum eclampsia. *Anesth Analg* 1996; **82**: 666–8.

14 Will AD, Lewis KL, Hinshaw DB. Cerebral vasoconstriction in toxaemia. *Neurology* 1987; **37**: 1555–7.

15 Horn EH, Filshie M, Kerslake RW, Jaspan T, Worthington BS, Rubin PC. Widespread cerebral ischaemia treated with nimodipine in a patient with eclampsia. *Br Med J* 1990; **301**. 79

16 Collier BB. Treatment for post dural puncture headache *Br J Anaesth* 1994; **72**: 366–7.

17 Foster PA. ACTH treatment for post lumbar puncture headache. *Br J Anaesth* 1994; **73**: 429.

18 Kshatri AM, Foster PA. Adrenocorticotrophic hormone infusion as a novel treatment for post-dural puncture headache. *Regional Anesth* 1997; **22**: 432–4.

19 Banks S, Paech M, Gurrin L. An audit of epidural blood patch after accidental dural puncture with a Tuohy needle in obstetric patients. *Int J Obs Anesth* 2001; **10**. 172–6

British Journal of Anaesthesia 89 (5): 786–87 (2002)

Anaesthesia in an adult with Rubenstein–Taybi syndrome using the ProSeal laryngeal mask airway

S. J. Twigg* and T. M. Cook

Department of Anaesthesia, Royal United Hospital, Combe Park, Bath BA1 2NG, UK
**Corresponding author*

We report the anaesthetic management of an adult with Rubenstein–Taybi syndrome. This rare congenital syndrome is characterized by severe learning difficulties, cardiac abnormalities, gastrooesophageal reflux, and cranio-facial abnormalities with the likelihood of difficult intubation. A ProSeal laryngeal mask airway was used to ventilate the patient for eye surgery.

Br J Anaesth 2002; **89**: 786–7

Keywords: complications, difficult intubation; complications, Rubenstein–Taybi syndrome; equipment, masks anaesthesia; gastrointestinal tract, gastroesophageal reflux

Accepted for publication: May 12, 2002

Rubenstein–Taybi syndrome (RTS) is a rare autosomal dominant genetic disorder first described in 1963.[1] The underlying abnormality is disruption of a gene on chromosome 16. Severe learning difficulty with progressive blindness and deafness is universal. Cranio-facial abnormalities suggest difficult tracheal intubation (Fig. 1).[2 3] Gastro-oesophageal reflux has been described and may lead to recurrent respiratory infections. Congenital heart disease is present in one-third of patients.[4] Administration of suxamethonium has been associated with multiple cardiac arrhythmias.[5] We describe the anesthetic management of an adult patient with RTS listed for bilateral phaecoemulsification and intra-ocular lens implants.

Case report

A 28-yr-old woman with RTS was seen before elective ophthalmic surgery. She suffered from severe learning difficulties, was deaf and had worsening vision because of cataracts. She was able to communicate by gestures. Her mobility was limited because of contraction deformities of the lower limbs, but she was able to feed and dress herself with help. Regurgitation of food was not reported, nor were recurrent respiratory infections. This suggested that she did not suffer from significant gastro-oesophageal reflux, although it was impossible to obtain a reliable history. Apart from ophthalmic and orthodontic problems she appeared to be in good health. She took no regular medication and had not had a previous anaesthetic.

Examination showed a woman of short stature (120 cm, 45 kg). She had a pronounced kyphoscoliosis. Her head was held flexed and extension of the neck was reduced, apparently by increased muscle tone. She had a small mandible, pronounced incisors, a high arched palate, and a high anterior larynx. The Mallampati airway grading as modified by Samsoon and Young was 3.[6 7] We predicted difficult intubation. Examination of the cardiovascular system was normal. A normal full blood count, electrolyte profile, and ECG were obtained. Chest x-ray showed the kyphoscoliosis with small lung fields and a normal cardiac outline.

We planned to ventilate the patient via a ProSeal laryngeal mask airway (PLMA[†]), (Laryngeal Mask Company, Henley on Thames, UK). We made sure that two experienced anaesthetists, and equipment necessary to manage a difficult airway, including fibreoptic bronchoscope, were immediately available.

The patient received a H_2 antagonist (nizatidine 150 mg), and a sedative (temazepam 20 mg), as premedication. Local anaesthetic cream (ametop) was applied to both hands. After non-invasive monitoring and a peripheral venous cannula had been placed, anaesthesia was induced with propofol 100 mg and fentanyl 50 μg. Adequate ventilation with a bag and mask was confirmed before a non-depolarizing neuromuscular blocking agent (atracurium 25 mg) was administered. We carried out laryngoscopy to ascertain the potential difficulty of future intubation, and the cords were partially seen (Cormack and Lehane Grade II view[8]). A size 4 PLMA was inserted and intermittent positive pressure ventilation was established. A size 14 orogastric tube was passed via the drainage tube of the PLMA and was aspirated. No fluid was obtained.

Anaesthesia was maintained with isoflurane 1% in 50% oxygen and nitrogen. Ventilation via the PLMA was readily achieved with inflation pressures less than 20 cm of water and with no evidence of gas leakage. The orogastric tube

---

[†] LMA® is the property of Intavent Limited

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

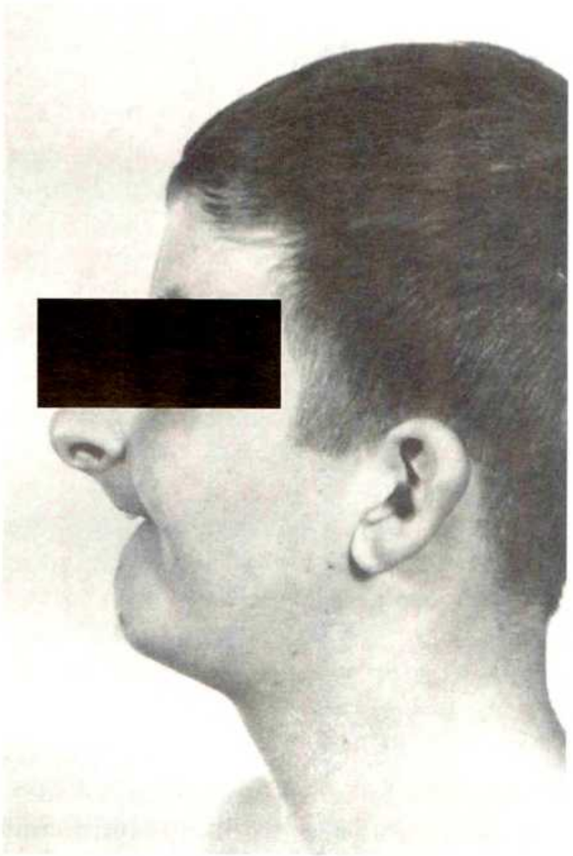

[redacted]

Fig 1 A similar patient with RTS, illustrating characteristic cranio-facial abnormalities. Reproduced with permission from the BMJ Publishing Group; Berry AC. Rubenstein–Taybi syndrome. *J Med Genet* 1987; **24**: 562–6.

was left in place to vent the stomach throughout the case. The patient had uneventful bilateral phaecoemulsification with intra-ocular lens implants. Neuromuscular block was antagonized at the end of surgery and the PLMA was removed with the orogastric tube after spontaneous breathing had returned. The patient made an uncomplicated recovery from anesthesia and was discharged from hospital later the same day.

Discussion

Whilst RTS is rare, patients may present when they require surgery for the correction of orthopedic, orthodontic, ophthalmic or cardiac lesions, or for incidental surgical conditions. We found no reports of the anaesthetic management of adults with RTS in English language journals. The associated problems pose significant difficulty for anaesthetic management. Difficult intubation and recurrent respiratory problems might initially suggest regional anaesthesia would be preferable for suitable cases, but communication difficulties are likely to hamper compliance with such techniques. For the same reason awake fibre-optic intubation would be unsuitable. The reported high incidence of gastro-oesophageal reflux suggests that a rapid sequence induction with suxamethonium would be prudent, but the report of adverse reaction to this drug would be against this.[5] Clearly, assessment must be made on an individual basis.

We considered difficult intubation as the biggest risk for this individual. However, the procedure planned was ophthalmic surgery for which the laryngeal mask airway is preferable from a surgical, anaesthetic, and patient perspective.[9] The patient we describe had no significant history of gastro-oesophageal reflux but we considered some protection from aspiration of stomach contents advisable. The PLMA offers a compromise between the two options. It is specifically designed for intermittent positive pressure ventilation unlike the standard or re-inforced LMA. The design aims to separate the respiratory and gastrointestinal tracts. The drain tube is designed to vent stomach contents and may, therefore, reduce the risk of regurgitation of stomach contents.[10] An orogastric tube may also be reliably passed via this lumen into the stomach.[11] In addition, the PLMA achieves a seal against the larynx that is approximately 50% higher than the classic LMA,[11 12] reducing the likelihood of failed or inadequate ventilation. Whilst this patient could have been safely anaesthetized in several ways, by using the PLMA we were able to reliably ventilate the patient, confirm that the stomach was empty, and still provide an LMA-based anaesthetic, which is desirable for such ophthalmic cases.

References

1 Rubenstein JH, Taybi H. Broad thumbs and facial abnormalities. *Am J Dis Child* 1963; **105**: 588–608
2 Stirt JA. Anaesthetic problems in Rubenstein–Taybi syndrome. *Anaesth Analg* 1981; **60**: 534–6
3 Critchley LA, Gin T, Stuart JC. Anaesthesia in an infant with Rubenstein–Taybi syndrome. *Anaesthesia* 1995; **50**: 37–8
4 Stevens CA, Bhakta MG. Cardiac abnormalities in the Rubenstein-Taybi syndrome. *Am J Med Genet* 1995; **59**: 346–8
5 Stirt JA. Succinylcholine in Rubenstein–Taybi syndrome. *Anesthesiology* 1982; **57**; 429
6 Mallampati SR, Gatt SP, Gugino LD, *et al.* A clinical sign to predict difficult tracheal intubation. *Can Anaesth Soc J* 1985; **32**: 429–34
7 Samsoon GLT, Young JRB. Difficult tracheal intubation: a retrospective study. *Anaesthesia* 1987; **42**: 487–90
8 Cormack RS, Lehane J. Difficult intubation in obstetrics. *Anaesthesia* 1984; **39**: 1105–11
9 Akhtar TM, McMurray P, Kerr WJ, Kenny GN. A comparison of laryngeal mask airway with tracheal tube for intra-ocular ophthalmic surgery. *Anaesthesia* 1992; **47**: 668–71
10 Keller C, Brimacombe J, Kleinsasser A, Loeckinger A. Does the ProSeal laryngeal mask airway prevent aspiration of regurgitated fluid. *Anaesth Analg* 2000; **91**: 1017–20
11 Cook TM, Nolan JP, Vergese C, *et al.* Randomized crossover comparison of the ProSeal with the classic laryngeal mask airway in unparalysed anaesthetized patients. *Br J Anaesth* 2002; **88**: 527–33
12 Keller C, Brimacombe J. Mucosal pressure and oropharyngeal leak pressure with the ProSeal *vs* laryngeal mask airway in anaesthetized paralysed patients. *Br J Anaesth* 2000; **85**: 262–6

British Journal of Anaesthesia **89** (**5**): 788–91 (2002)

General anaesthesia in a patient with Brugada syndrome

C. J. Edge[1]*, D. J. Blackman[2], K. Gupta[1] and M. Sainsbury[1]

[1]*Nuffield Department of Anaesthetics and*
[2]*Department of Cardiology, Oxford Radcliffe Hospitals Trust, Oxford, OX3 9DU, UK*
**Corresponding author*

The successful administration of a combined general and epidural anaesthetic to a patient with Brugada syndrome is reported. A review of the literature is presented.

Br J Anaesth 2002; **89**: 788–91

Keywords: complications, Brugada syndrome

Accepted for publication: July 5, 2002

We describe the successful administration of a combined general and epidural anaesthetic for laparotomy in a patient with Brugada syndrome.[1]

Case report

A 52-yr-old man presented with acute small bowel obstruction for a laparotomy. Eighteen months before admission, the patient had suffered an unheralded episode of a pulseless cardiac arrhythmia (recognized by a relative trained in basic life support) at home. Recovery occurred after basic cardiopulmonary resuscitation, before the arrival of the paramedic ambulance crew. A further episode of monitored ventricular fibrillation (VF) in the ambulance required a single 200 J cardioversion. He had no history of angina or previous syncope and there was no family history of sudden death. His father had suffered a myocardial infarction at the age of 50 and died. The patient had been a smoker until 3 months before admission and had a history of peptic ulcer that had been treated with ranitidine.

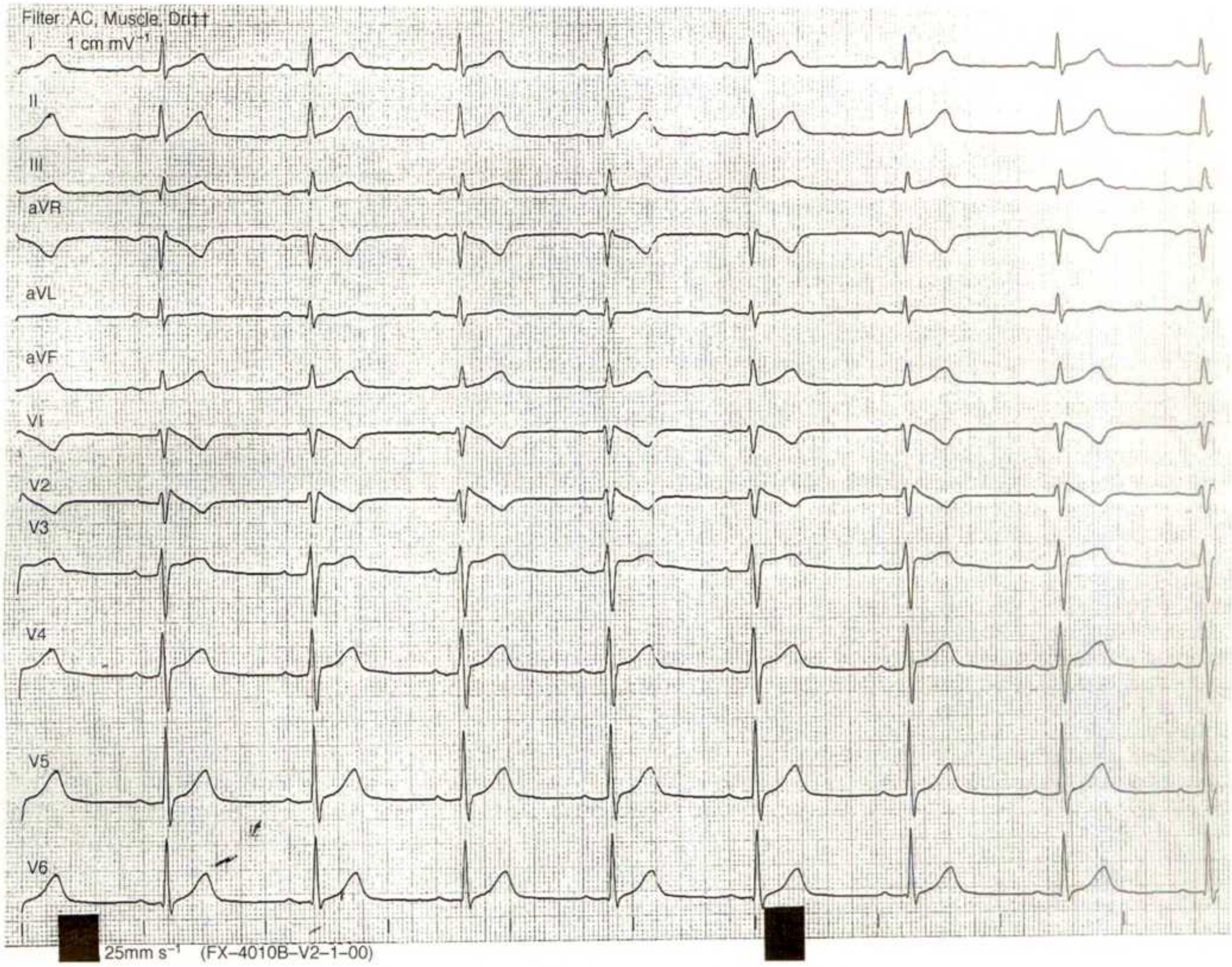
On investigation, the patient had a 12-lead ECG showing a partial right bundle branch block with a 'coved' pattern of ST elevation in leads V_1 to V_3 (Fig. 1). Cardiac enzymes were not elevated. Subsequent cardiac catheterization showed normal left ventricular function and coronary arteries. The patient underwent a flecainide challenge with an i.v. bolus of 150 mg. This produced accentuation of the ST elevation, consistent with Brugada syndrome. In view of the documented VF arrest, characteristic ECG features, and the absence of underlying structural heart disease, a diagnosis of Brugada syndrome was made. A single-chamber implantable cardioverter–defibrillator (ICD) was inserted under local anaesthesia and sedation. The patient was discharged home on aspirin, ranitidine, nadolol (subsequently changed to bisoprolol) and amiloride.

Before arrival in the anaesthetic room during this admission, the question of postoperative analgesia was discussed with the patient. Having been informed of the various options and their associated risks, the patient consented to the placement of a thoracic epidural catheter after induction of general anaesthesia. After the patient had arrived in the anaesthetic room, and with the patient fully monitored, the ICD was externally disabled. A right radial arterial cannula and a right internal jugular triple-lumen cannula were inserted under local anaesthetic. The patient underwent rapid sequence induction with thiopental 5 mg kg^{-1} and succinylcholine 100 mg. After intubation of the trachea, the patient was given fentanyl 100 µg and a thoracic epidural catheter was inserted aseptically at the T8/9 space with the patient in the left lateral position. Cefuroxime 1.5 g, metronidazole 500 mg and gentamicin 320 mg were then administered. Anaesthesia was maintained using an oxygen–nitrous oxide–isoflurane mixture with increments of vecuronium 2 mg for neuromuscular block. Epidural analgesia was provided with 0.25% bupivacaine 10 ml and fentanyl 20 µg. An external defibrillator, connected to defibrillation pads placed on the patient, was present in theatre during the laparotomy. At operation, some minor small bowel adhesions were divided. No other abnormality was found. Neostigmine 2.5 mg–glycopyrrolate 0.5 mg solution was used at the end of the procedure to antagonize the neuromuscular block. Continual monitoring of the ECG showed no abnormalities as a result of the anaesthetic or the operation. The internal defibrillator was re-enabled in the recovery room, and the patient went on to recover successfully from the operation.

Discussion

Brugada syndrome is characterized by an ECG pattern of right bundle branch block and ST segment elevation in the

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002



[redacted]

[redacted]

Fig 1 Resting 12-lead ECG showing a characteristic pattern of right bundle branch block with 'coved' ST elevation in leads V_1 to V_3.

right precordial leads (V_1 to V_3), without evidence of underlying structural heart disease. It is associated with a significant risk of ventricular tachyarrhythmias and sudden death. It was first recognized as a distinct clinical entity in 1992.[1] The syndrome is familial (although this was not observed in our patient), with an autosomal dominant mode of transmission and incomplete penetrance. Arrhythmic events are observed at an average age of approximately 40 yr, but have been reported over a wide range of ages from 2 to 77 yr.[2]

Establishing the diagnosis of Brugada syndrome can be difficult. The electrocardiographic signature is concealed in up to 30% of affected individuals[3] and can only be seen after administration of potent sodium channel blockers, such as flecainide, propafenone and procainamide.[4] However, recent follow-up data indicate that the risk of ventricular tachyarrhythmias is low in the absence of a resting ECG abnormality.[5] In patients with an abnormal resting ECG, electrophysiological study incorporating programmed electrical stimulation is recommended to further define the risk of malignant tachyarrhythmia. In the presence of inducible VT/VF, the risk of sudden death is 5–10% per year and ICD implantation is recommended, as it is in any Brugada patient with a history of documented VT/VF or resuscitated cardiac arrest.

The molecular basis for the ventricular arrhythmias remains uncertain. Mutations have been identified in patients with Brugada syndrome in the *SCN5A* gene, which codes for the tetrodotoxin-'insensitive' human cardiac sodium channel (hH1).[6] The functional abnormalities of the expressed mutant channels are opposite to those found in sodium channel mutants associated with long-QT syndrome. In Brugada syndrome, as in some of the other idiopathic ventricular fibrillation syndromes, the sodium channels show loss-of-function features, such as enhanced inactivation.[7] However, it is difficult to see how these features give rise to ventricular arrhythmias. A clue may come from the finding that calmodulin, a ubiquitous calcium-sensing protein, binds to the carboxy-terminal IQ domain of the hH1 channel in a calcium-dependent manner.[8] A naturally occurring mutation (A1924T) in the IQ domain alters hH1 function in a manner characteristic of the Brugada syndrome, but at the same time inhibits slow inactivation induced by calcium–calmodulin, yielding a clinically benign (arrhythmia-free) phenotype. Further studies will be required to elucidate the precise mechanism(s) by which the other mutations in hH1 give rise to Brugada syndrome.

So far as we can ascertain, this is only the third report of a general anaesthetic having been administered to a patient with Brugada syndrome. The first case report[9] describes a 47-yr-old Japanese male undergoing hemilaminectomy. Anaesthesia was induced with fentanyl 50 µg, droperidol 2.5 mg and propofol 120 mg, and the neuromuscular blocking drug used was vecuronium 8 mg. Maintenance of anaesthesia continued with the use of sevoflurane and further fentanyl 150 µg. Antagonism of the neuromuscular block was accomplished using neostigmine 2.5 mg and atropine 1.0 mg; during antagonism the authors noted an elevation of the ST segments on the ECG.

A second case report[10] describes a 49-yr-old man with Brugada syndrome who had surgery for a polyp on the vocal cords. Despite episodes of vertigo and an ECG showing a right bundle branch block with elevation of the ST segments in leads V_1 and V_2, the cardiologist did not consider that there was an indication for an ICD. The patient was given diazepam 10 mg orally as a premedication and monitored using ECG, a non-invasive blood pressure cuff, pulse oximetry and capnography. Induction of anaesthesia was carried out using fentanyl 0.2 mg, propofol 200 mg, mivacurium 18 mg and glycopyrrolate 0.3 mg. A portable defibrillator was placed in theatre in case ventricular dysrhythmias developed. Anaesthesia was maintained using 1% isoflurane with a nitrous oxide–oxygen gas mixture. After surgery, the patient was transferred to the recovery room and monitored for 2 h. No problems were reported with this anaesthetic.

Both sets of authors in these case reports note that the administration of drugs that block sodium channels, such as procainamide and flecainide, are contraindicated in patients with Brugada syndrome.

Miyazaki and colleagues[11] describe four patients who underwent investigation for Brugada syndrome. They noted that selective α-adrenoceptor stimulation by i.v. norepinephrine in the presence of propranolol or by i.v. methoxamine consistently augmented ST segment elevation whereas α-adrenoceptor block reduced it in three of the patients. Additionally, i.v. neostigmine and class IA antiarrhythmic drugs augmented ST elevation without inducing coronary spasm, but class IB antiarrhythmic drugs had no effect on ST elevation. However, the number of patients was very small and it is difficult to draw firm conclusions from this study, especially in the light of the heterogeneous nature of the mutations leading to Brugada syndrome.

In the case described by Lafuente Martin and colleagues[10] and in our case, isoflurane was administered as an anaesthetic agent. It is perhaps surprising (and illustrates the lack of detailed understanding of the physiology and pharmacology behind Brugada syndrome) that no cardiac arrhythmias were detected during anaesthesia in these cases, in the light of recent evidence suggesting that isoflurane should be avoided in patients with prolonged QT_c syndrome.[12]

Administration of i.v. neostigmine with glycopyrrolate in our patient did not give rise to any detectable cardiac arrhythmia. Likewise, bupivacaine given via the epidural route did not cause problems. However, in view of the fact that drugs that block the sodium channels may cause problems in patients with Brugada syndrome, it may be wise in future to avoid systemic administration of local anaesthetics by routes that cause a rapid increase in serum concentrations of local anaesthetic.

Reported experience of general anaesthesia in Brugada syndrome is limited at present. However, it is an increasingly recognized disorder, and one which many anaesthetists are likely to encounter in their clinical practice in the future. Caution should be exercised when using α-agonists or neostigmine, while class I antiarrhythmic drugs must be avoided. In any patient with an ICD, the device must be disabled immediately before surgery. Close cooperation of the anaesthetist with a cardiologist is essential both before and after surgery. In patients with Brugada syndrome in whom no ICD has been fitted, recovery should take place in either a coronary care unit or a high-dependency unit. This will permit detection and treatment of cardiac arrhythmias, which are most likely to occur in the postoperative period,[13] in a timely manner.

References

1 Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome: a multicenter report. *J Am Coll Cardiol* 1992; **20**: 1391–6

2 Priori SG, Napolitano C, Giordano U, Collisani G, Memmi M. Brugada syndrome and sudden cardiac death in children. *Lancet* 2000; **355**: 808–9

3 Brugada R, Brugada J, Antzelevitch C, *et al.* Sodium channel blockers identify risk for sudden death in patients with ST-segment elevation and right bundle branch block but structurally normal hearts. *Circulation* 2000; **101**: 510–5

4 Priori SG, Napolitano C, Gasparini M, *et al.* Clinical and genetic heterogeneity of right bundle branch block and ST-segment elevation syndrome: a prospective evaluation of 52 families. *Circulation* 2000; **102**: 2509–15

5 Brugada J, Brugada R, Antzelevitch C, Towbin J, Nademanee K, Brugada P. Long-term follow-up of individuals with the electrocardiographic pattern of right bundle-branch block and ST-segment elevation in precordial leads V_1 to V_3. *Circulation* 2002; **105**: 73–8

6 Rook MB, Bezzina Alshinawi C, Groenewegen WA, *et al.* Human SCN5A gene mutations alter cardiac sodium channel kinetics and are associated with the Brugada syndrome. *Cardiovasc Res* 1999; **44**: 507–17

7 Balser JR. Sodium 'channelopathies' and sudden death: must you be so sensitive? *Circ Res* 1999; **85**: 872–4

8 Tan HL, Kupershmidt S, Zhang R, *et al.* A calcium sensor in the sodium channel modulates cardiac excitability. *Nature* 2002; **415**: 442–7

9 Sugi Y, Mori M, Ono M, Kurihara Y. Anesthetic management of a patient with Brugada syndrome. *Masui Jpn J Anesthesiol* 2000; **49**: 884–6

10 Lafuente Martin FJ, Pascual Bellosta A, Abengochea Belsty JM, Fraca Cardiel C, Sanchez Tirado JA, Urieta Solanas JA. Brugada syndrome and anesthesia: a case report. *Rev Esp Anestesiol Reanim* 1998; **45**: 301–2

11 Miyazaki T, Mitamura H, Miyoshi S, Soejima K, Aizawa Y, Ogawa S. Autonomic and antiarrhythmic drug modulation of ST segment elevation in patients with Brugada syndrome. *J Am Coll Cardiol* 1996; **27**: 1061–70

12 Guler N, Kati I, Demirel CB, Bilge M, Eryonucu B, Topal C. The effects of volatile anesthetics on the Q–T_c interval. *J Cardiothorac Vasc Anesth* 2001; **15**: 188–91

13 O'Kelly B, Browner WS, Massie B, Tubau J, Ngo L, Mangano DT. Ventricular arrhythmias in patients undergoing noncardiac surgery. The Study of Perioperative Ischemia Research Group. *JAMA* 1992; **268**: 217–21

British Journal of Anaesthesia 89 (5): 792–5 (2002)

BJA

COMMENTARY

Preoperative use of herbal medicines: a patient survey

C. M. Skinner[1]* and J. Rangasami[2]

[1]Royal Berkshire Hospital, Reading, UK. [2]Department of Anaesthesia, Wexham Park Hospital, Wexham Street, Slough, Berkshire SL2 4HL, UK

**Corresponding author*

Background. There has been recent concern in the media over the possible detrimental effects of herbal medicines on the perioperative period. Perceived by the public as 'natural' and therefore safe, herbal remedies may have led to adverse events such as myocardial infarction, bleeding, prolonged or inadequate anaesthesia and rejection of transplanted organs. In addition, herbal remedies can interact with many drugs given in the perioperative period. In this article we summarize the potential perioperative complications that can occur.

Methods. In order to determine the extent of use of herbal medicines, we conducted a survey of patients presenting for anaesthesia. During a 3-month period, patients were directly asked by anaesthetic staff if they were currently self-administering herbal medication.

Results. Of 2723 patients, 131 (4.8%) were taking one or more herbal remedy. In only two cases was this recorded in the patients' notes. Women and patients aged 40–60 yr were most likely to be taking a herbal product ($P<0.05$ and $P<0.001$ respectively). The most commonly used compounds were, in descending order, garlic, ginseng, ginkgo, St John's wort and echinacea.

Conclusion. Self-administration of herbal medicines is common in patients presenting for anaesthesia. Because of the potential for side-effects and drug interactions it is important for anaesthetists to be aware of their use.

Br J Anaesth 2002; **89**: 792–5

Keywords: complications, herbal medicines; interactions (drug)

Accepted for publication: July 5, 2002

There has been increasing concern in the American medical press about the potential complications arising in the perioperative period as a result of patients' use of complementary medicines.[1] The assumption by patients and doctors that these products 'are natural and therefore safe' is clearly dangerous. Morbidity and mortality are more likely in the perioperative period because of the polypharmacy and assaults on normal physiology that occur.[2] Such complications may include myocardial infarction,[3] bleeding,[4 5] prolonged[6] or inadequate anaesthesia[7] and organ transplant rejection.[8]

The exact degree of cause for concern remains unclear. Very few of the huge number of herbal remedies have been formally researched and therefore most information is pooled from case reports and other anecdotal evidence.

In Table 1 we summarize the most commonly used herbal remedies together with their possible modes of action and perioperative complications.[5–7 9–24]

There appears to be increasing public interest in the use of complementary medicine. In the USA the self-prescribing of herbal medicines in the presurgical patient has been studied. Tsen and colleagues reported the use of herbal remedies in 22% of presurgical patients[25] and in a similar study Kaye and colleagues reported 32%.[26] More than 70% of these patients failed to disclose their use of herbal medicines to their attending anaesthetist.

It remains to be seen if the enthusiasm for such remedies is as high in this country. The aim of this study was to quantify the use of herbal remedies in patients attending for anaesthesia in a British district general hospital.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Table 1 Pharmacological effects and potential perioperative complications of eight commonly used herbal remedies

Name of herb	Common uses	Pharmacological effects	Potential perioperative complications
Echinacea, purple coneflower root	Prophylaxis and treatment of viral, bacterial and fungal infections	Stimulation of the immune system.[9] With long term use may be immunosuppressive[10]	Reduced effectiveness of immunosuppressants [11] Potential for wound infection with long-term use [10] May cause hepatotoxicity especially when used with other hepatotoxic drugs[12]
Ephedra, ma huang	Diet aid	Indirectly and directly acting sympathomimetic[13]	Dose-dependent increase in heart rate and blood pressure with potential for perioperative myocardial infarction and stroke [14] Arrythmias with halothane Tachyphylaxis with intraoperative ephedrine
Garlic, ajo	Antihypertensive, lipid-lowering agent, anti-thrombus-forming	Inhibits platelet aggregation (partially irreversibly) in a dose-dependent manner [15] Lowers serum lipid and cholesterol levels[16]	May potentiate other platelet inhibitors Concerns for perioperative bleeding Concerns for neuraxial blockade
Ginkgo, maidenhair, fossil tree	Circulatory stimulant Used to treat Alzheimer's disease, peripheral vascular disease and erectile dysfunction	Inhibits platelet activating factor [17] Antioxidant [18] Modulates neurotransmitter activity	Concerns for perioperative bleeding.[5] [19] May potentiate other platelet inhibitors
Ginseng, ajo	To protect the body against stress and restore homeostasis	Poorly understood. Possible similar mechanism to steroid hormones. Inhibits platelet aggregation (partly irreversibly).[20] Prolongs activated partial thromboplastin time.[21]	Potential to increase perioperative bleeding. Potential for hypoglycaemia
Kava, ava pepper	Anxiolytic	Possible potentiation of γ-aminobutyric acid (GABA) transmission[22]	Potentiates sedative effects of anaesthetic agents [6] Possible withdrawal syndrome after sudden abstinence Recent reports of kava-induced hepatotoxicity to the medicines control agency
St John's wort, goatweed, amber, hardhay	Treatment for depression and anxiety	Central inhibition of serotonin, noradrenaline and dopamine [23] Induction of cytochromes 450 3A4 and P450 2C9[7]	Decreased effectiveness of cyclosporin, alfentanil, midazolam, lignocaine, calcium channel blockers and digoxin[7]
Valerian, vandal root, all heal	Anxiolytic and sleep aid	Potentiation of GABA neurotransmission[24]	Potentiates sedative effects of anaesthetic agents. Withdrawal-type syndrome with sudden abstinence

Method

During a 3-month period, operating department practitioners and anaesthetic nursing staff questioned all patients about their current use of herbal remedies immediately before administration of anaesthesia. The questioning formed part of the routine preoperative checklist and asked if the patient was presently taking, or at some point in the last 2 weeks had taken, herbal medication.

A list of 16 commonly used medications was made available to the patient and questioner to act as a guide, as not all the questioners were familiar with herbal remedies. However, if the patient was taking another form of alternative medicine not mentioned on the list this was also recorded. Vitamins and minerals were not included in this survey. Non-English speakers were excluded from questioning.

The questionnaire recorded age, sex and the name(s) of the herbal medicines currently taken. In the case of patients taking such remedies, their notes were examined retrospectively for any mention of the herbal medicine in the preassessment clerking or drug information section of the anaesthetic form.

Results were tabulated and analysed using appropriate descriptive statistical analysis. Differences with respect to the influences of patient sex and patient age on the prevalence of herbal medication use were tested by using χ^2 analysis. A P value of <0.05 was considered statistically significant.

Results

During the 3-month period, 3349 patients underwent anaesthesia at Wexham Park Hospital. Forms were received from 2723, giving a response rate of 81.3%.

A total of 131 patients reported the use of herbal medications (4.8%). Eighty-three patients were taking a single herbal remedy and 48 patients were taking more than one. Of these patients, 42 reported using two herbal

Table 2 Age groups

Age (yr)	Taking herbal medication (A)	Not taking herbal medication	Total (B)	% (A/B)
≤30	18	655	673	2.7%
31–40	20	283	303	6.6%
41–50	34	358	392	8.7%
51–60	32	348	380	8.4%
61–70	17	435	452	3.8%
>70	10	513	523	1.9%

Table 3 Types of herbal medication used

Medication	Number using	% of all patients	% of total number of herbal medications used
Arnica	3	0.11	1.6
Echinacea	19	0.70	10.1
Ephedra	3	0.11	1.6
Garlic	43	1.58	22.9
Ginkgo	30	1.10	16.0
Ginseng	34	1.25	18.1
Kava	1	0.03	0.5
Primrose	11	0.40	5.9
Red clover	2	0.07	1.1
Saw palmetto	5	0.18	2.7
St John's wort	27	0.99	14.4
Valerian	10	0.37	5.3
Total	188	4.81	

medicines, four reported using three, one reported using four and one reported using five remedies. Female patients (80 out of 1387) used herbal medicines more frequently than males (51 out of 1336; $\chi^2=5.65$, $P<0.05$) (Table 2).

Our data indicate an influence of age on the prevalence of herbal medication use (Table 2).

The most commonly used medications reported are shown in Table 3. Garlic, ginseng, ginkgo, St John's wort and echinacea were the most frequently reported remedies in order of highest to lowest.

In only two cases was there written documentation of the patient's use of herbal remedies in the medical notes. In both cases the documentation was in the preassessment clerking. There were no records of the patients' use of herbal preparations on any anaesthetic forms.

Discussion

Our survey showed that substantially fewer patients are self-administering herbal remedies when compared with similar surveys carried out in the USA. However, it remains that a significant proportion of the presurgical population are taking potentially harmful medications without the knowledge of their anaesthetist.

Although the pharmacodynamics and pharmacokinetics of the majority of these remedies have yet to be fully clarified, reports of adverse events in the perioperative period suggest their importance and certainly that anaesthetists should become more aware of their use.

In the UK the majority of herbal medicines are exempt from the licensing requirements set out in Section 12 of the Medicines Act 1968.[27] Approximately 20% of companies choose to seek a licence as a sign of a higher quality product. This process, however, is long and expensive and it can prove difficult to meet conventional requirements to prove product efficacy. In addition, herbal medicines cannot be patented, and this further removes the incentive to undertake costly research. In effect, this leaves the vast majority of herbal remedies exempt from the safety and efficacy requirements and regulations that prescription-only and over-the-counter drugs must fulfil (i.e. preclinical animal studies, controlled clinical trials and post-marketing surveillance). This current lack of regulation of herbal medicines also allows the potency of the herbal content to vary from manufacturer to manufacturer.[28] This can therefore lead to significant variations in the pharmacological effects of a given remedy.

Despite the exemption from regulatory laws, in October 1996 the Yellow Card Scheme [the voluntary, spontaneous adverse drug-reaction reporting scheme run by the Committee on Safety of Medicines (CSM/Medicines Control Agency UK)] was extended to include reporting of suspected adverse reactions to unlicensed herbal medicines. As of May 28, 2002, the CSM/Medicines Control Agency had received 1260 reports of adverse reactions that were suspected to be associated with herbal medicines via the Yellow Card Scheme. Of these, 31 had a fatal association (CSM, personal communication).

In addition, at the international level, 5000 suspected reactions were reported to the WHO before 1996,[29] and between 1993 and 1998 a further 2621 adverse events, including 101 deaths, were reported to the US Food and Drugs Administration.[30] Of concern is that there is no doubt that these figures are grossly underestimated, as medical staff are often ignorant of the pharmacology of these medications.

In our survey there was no documentation of herbal medications on the anaesthetic forms of patients using such products. We must assume that this was because either the patients or their anaesthetists did not consider them to be of importance. We believe that anaesthetists should elicit and document a full drug history, including the use of herbal remedies, in every patient.

Because pharmacokinetic data are lacking, the American Society of Anesthesiologists recommends that patients discontinue use of herbal medications 2–3 weeks before surgery.[31] [32] However, it remains that many patients will still be taking herbal remedies before surgery, either because they are unaware of this recommendation, or because they are presenting for non-elective surgery. This means that all anaesthetists must familiarize themselves with the potential perioperative complications that can occur with the commonly used remedies. Anticipating a possible reaction is better than reacting to an unexpected condition.

Acknowledgements

We acknowledge the help of Miss Claire Davies (senior pharmacovigilance scientist) and Miss Lesley Curwen (scientific assessor, Pharmacoviligance Group Post Licensing Division) of the Medicines Control Agency.

References

1 Ang-lee MK, Moss J, Yuan C-S Herbal medicines and perioperative care. *JAMA* 2001; **286**. 208–216

2 Bovil JG. Adverse drug reactions in anaesthesia. *J Clin Anesth* 1997; **9** (Suppl 6): 3S–13S

3 Haller CA, Benowitz NL. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. *N Engl J Med* 2000; **343**: 1833–8

4 Rose KD, Croissant PD, Parliament CF, Levin MB. Spontaneous spinal epidural haematoma with associated platelet dysfunction from excessive garlic ingestion. *Neurosurgery* 1990; **26**: 880–2

5 Fessenden JM, Wittenborn W, Clarke L. Ginkgo biloba. a case report of herbal medicine and bleeding postoperatively from a laparoscopic cholecystectomy *Am Surg* 2001; **67**: 33–35

6 Almeida JC, Grimsley EW. Coma from the health food store: interaction between kava and alprazolam. *Ann Intern Med* 1996; **125**· 940–1

7 Ernst E. Second thoughts about the safety of St John's wort. *Lancet* 2000; **354**· 2014–6

8 Breidenbach T, Hoffman MW, Becker T, Schlitt H, Klempnauer J. Drug interaction of St. John's wort with cyclosporin. *Lancet* 2000; **355**: 1912

9 See DM, Broumand N, Sahl L, Tilles JG *In vitro* effects of Echinacea and ginseng on natural killer and antibody-dependent cell cytotoxicity in healthy subjects and chronic fatigue syndrome or acquired immunodeficiency syndrome patients. *Immunopharmacology* 1997; **35**: 229–35

10 Boullata JI, Nace IS. Safety issues with herbal medicine *Pharmacotherapy* 2000; **20**: 257–69

11 Pepping J. Echinacea. *Am J Health Syst Pharm* 1999; **56**. 121–122

12 Miller LG. Herbal medicinals: selected clinical considerations focusing on known or potential drug-herb interactions. *Arch Intern Med* 1998; **158**: 2200–11

13 Gurley BJ, Gardener SF, Hubbard MA. Content versus label claims in ephedra-containing dietary supplements. *Am J Health Syst Pharm* 2000; **57**: 963–9

14 Nightingale SL From the Food and Drug Administration. *JAMA* 1997; **278**: 15

15 Srivastava KC. Evidence for the mechanism by which garlic inhibits platelet aggregation. *Prostaglandins Leukot Med* 1986, **22**· 313–21

16 Stevinson C, Pittler MH, Ernst E. Garlic for treating hypercholesterolaemia: a meta-analysis of randomized clinical trials. *Ann Intern Med* 2000; **133**· 420–9

17 Chung KF, Dent G, McCusker M, Guinot P, Page CP, Barnes PJ Effect of ginkgolide mixture (BN 52063) in antagonizing skin and platelet responses to platelet activating factor in man *Lancet* 1987; **1**: 248–51

18 Maitra I, Marcocci L, Droy-Lefaix MT, Packer L. Peroxyl radical scavenging activity of Ginkgo biloba extract EGb 761 *Biochem Pharmacol* 1995; **49**. 1649–55

19 Vale S. Subarachnoid haemorrhage associated with Ginkgo biloba. *Lancet* 1998; **352**: 36

20 Kimura Y, Okuda H, Arichi S. Effects of various ginseng saponins on 5-hydroxytryptamine release and aggregation in human platelets. *J Pharm Pharmacol* 1988, **40**. 838–43

21 Park HJ, Lee JH, Song YB, Park KH Effects of dietary supplementation of lipophilic fraction from Panax Ginseng on cAMP and cGMP in rat platelets and on blood coagulation. *Biol Pharm Bull* 1996; **19**: 1434–9

22 Pepping J. Kava: Piper methysticum *Am J Health Syst Pharm* 1999; **56**: 957–8, 60

23 Shelton RC, Keller MB, Gelenberg A, *et al*. Effectiveness of St John's wort in major depression *JAMA* 2001; **285**· 1978–86

24 Ortiz JG, Nieves-Natal J, Chavez P. Effects of *Valeriana officinalis* extracts on flunitrazepam binding, synaptosomal GABA uptake and hippocampal GABA release. *Neurochem Res* 1999; **24** 1373–8

25 Tsen LC, Segal S, Pothier M, Bader AM. Alternative medicine use in presurgical patients *Anesthesiology* 2000; **93**. 148–51

26 Kaye AD, Clarke RC, Sabar R, *et al* Herbal medications current trends in anaesthesiology practice—a hospital survey. *J Clin Anesth* 2000; **12**: 468–71

27 Medicines Control Agency. Licensing of medicines: Policy on herbal medicines. Available at http://www.mca.gov uk/ourwork/licensingmeds/herbalmeds.htm

28 Consumer Reports. Herbal roulette *Consumer Rep* 1995, (November): 698–705

29 Edwards R. Monitoring the safety of herbal medicine. WHO project is under way. *Br Med J* 1995; **311**: 1569–70

30 Consumer Reports. Herbal Rx—the promises and pitfalls *Consumer Rep* 1999; (March)· 44–8

31 Leak JA. Herbal medicines: what do we need to know? *ASA Newsletter* 2000; 64

32 American Society of Anesthesiologists Anesthesiologists warn· if you're taking herbal products, tell your doctor before surgery. Available at. http·//www.asahq.org/PublicEducation/herbal.html

British Journal of Anaesthesia 89 (5): 796–801 (2002)

Correspondence

Recruitment manoeuvres on high frequency oscillation ventilation

Editor—We read with interest the recent article on high frequency oscillation in adolescents by Moganasundram and colleagues.[1]

The article raises a number of issues regarding the initiation and use of high frequency oscillatory ventilation (HFOV) not just in adolescents but also in adults.

In our unit we have used HFOV for over 3 yr on more than 70 patients. Through experience, we have found that recruiting in a stepwise fashion whilst connected to the oscillator has resulted in better haemodynamic stability and oxygenation. We use the Sensormedics 3100B (Yorba Linda, CA). All patients are connected with a closed suction system (Vygon, Cirencester, UK) in place, to prevent derecruitment with an $F\mathrm{I}_{\mathrm{O}_2}$ of 1.0 and an amplitude (ΔP) of 0, on a bias flow of 40 litre min^{-1}. Mean airway pressure is then adjusted to 40 cm H_2O and maintained for 40 s. The alarm on the Sensormedics 3100B can be silenced for 45 s and is therefore ideal for timing the duration of the recruitment manoeuvre. We use this pressure and duration from the evidence produced in Amatos' study.[2] However, we are aware of the problems of defining optimal lung inflation.

The mean airway pressure is then reduced to 30 cm H_2O on an $F\mathrm{I}_{\mathrm{O}_2}$ of 1.0 and the $F\mathrm{I}_{\mathrm{O}_2}$reduced every 2 min till either an $F\mathrm{I}_{\mathrm{O}_2}$ of 0.4 is obtained or the saturations are 88–93%. If the $F\mathrm{I}_{\mathrm{O}_2}$cannot be reduced to <0.6, then another recruitment manoeuvre is performed to 40 cm H_2O for 40 s on a $F\mathrm{I}_{\mathrm{O}_2}$of 1.0, but only reducing the mean airway pressure to 35 cm H_2O. The process is again repeated and if an $F\mathrm{I}_{\mathrm{O}_2}$of 0.6 still cannot be obtained then the recruitment manoeuvre is repeated but at a pressure of 50cm H_2O for 40 s. If during recruitment any patient shows signs of haemodynamic instability, the manoeuvre is abandoned and the patient's preload is optimized using the PiCCO system (Pulsion Medical Systems, Munich, Germany).

In our experience this technique gives a more controlled recruitment without using repeated disconnections starting at lower pressures than the manual procedures applied by Moganasundram and colleagues[1] using the Mapleson C circuit. It therefore allows more control over haemodynamic stability and oxygenation. This stepwise recruitment manoeuvre avoids any risk of derecruitment on disconnection and in theory any damage to the tracheal tube during clamping. Also it is more useful in patients with tracheostomies *in situ* who will not be able to have their tubes clamped.

We also question the use of the prone position in these patients on HFOV for a number of reasons. First, while in small children and neonates the process of turning the patient prone may be carried out safely and with ease, the process in large adults significantly increases the risk of iatrogenic complications.[3] Second, in our experience, the prone position on HFOV does not improve gas exchange if the patients have been adequately recruited initially. Recent evidence has also shown no improvement in outcome in those patients who have been placed prone on conventional ventilation.[4]

The greater frequencies used by Moganasundram and colleagues[1] (6–8 Hz) may reflect their experience with the paediatric population, but in our experience have resulted in significant air trapping and hypercapnia. We tolerate a pH >7.25 and manipulate this initially by increasing the amplitude (ΔP) to a maximum of 90 cm H_2O and then decreasing the frequency to a minimum of 4 Hz to control the pH. Recent evidence has also suggested that the Pa_{CO_2}level may have a prognostic value, as survivors have demonstrated a significant reduction in Pa_{CO_2}levels compared to non-survivors.[5]

Once again, the timing of intervention with HFOV has been brought to our attention and we agree it should no longer be used as a last resort or 'rescue therapy' but early to avoid further lung injury.[6] We currently institute HFOV for those patients at risk of developing further acute lung injury and feel that it is an extremely useful tool in the management of ARDS. We await with interest the results of the controlled trials currently in progress.

R. G. Roberts
N. J. Stallard
P. Morgan
Cardiff, UK

Editor—Thank you for the opportunity to reply to Roberts and colleagues. Roberts' group have extensive experience with high frequency oscillation (HFO) in adults and describe an oscillator-based recruitment manoeuvre starting at 40 cm H_2O, similar to that described by Amato.[2] We concede that there is no consensus as to the ideal recruitment manoeuvre whilst on HFO. However, Roberts' comment that their technique provides a 'more controlled recruitment starting at lower pressures' is clearly not borne out by our data. Table 1 in our paper[1] shows that our patients had initial mean airway pressures of 33, 26 and 40 cm H_2O with corresponding maximum recruitment pressures of 38, 31 and 45 cm H_2O. Also, the claim to 'better haemodynamic stability and oxygenation' is difficult to sustain without hard data.

We would agree that repeated disconnection for suctioning runs a risk of derecruitment. However, in our experience the frequency of suctioning on HFO is reduced compared to conventional ventilation, possibly as a result of better carbon dioxide clearance with HFO. Furthermore, we would advocate caution when considering the closed suction system advocated by Roberts. This system is purported to avoid alveolar collapse during conventional ventilation;[7] however, extreme negative pressure levels can result when suction flow is higher than ventilator flow.[8] The significance of this may be amplified during the active expiratory (negative pressure) phase during HFO. Also, on introduction of the suction catheter into the tracheal tube, there is an increase in end-expiratory pressure that can reach more than 10 cm H_2O above the set extrinsic positive end-expiratory pressure.[8] The literature is lacking in information on the use of closed suction systems with high frequency oscillatory ventilation.

We have not encountered damage to the tracheal tubes during clamping, probably as a consequence of the infrequency of suctioning and the positioning of protective gauze between the clamp and the tracheal tube. This technique is obviously not suitable for the tracheostomized patient. However, this practice is not common in paediatrics.

We were somewhat surprised at the view taken by Roberts about prone positioning in the management of acute respiratory distress syndrome. First, we do not think it is correct to extrapolate the iatrogenic problems multi-trauma patients suffer in the process of turning them prone to the rest of the acute respiratory distress syndrome population. Second, the fact that prone positioning improves oxygenation has been well established since its introduction in 1976.[9] To state that the improvement in oxygenation with prone positioning is not associated with a decrease in mortality on the basis of a single trial may be premature.[4] Gattinoni's trial had several methodological problems: (i) the trial was stopped early because of reluctance by staff

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

to forgo the prone position, resulting in decreased power; (ii) the patients were placed prone for only 7 h each day. Furthermore, other outcome measures such as duration of ventilation and length of hospital stay were not addressed.[4]

A final comment on our methodology relates to the relatively high frequencies (6–8 Hz) used. We have not experienced significant air trapping as a result of these frequencies. Also, as tidal volume and frequency bear an inverse relationship,[10] small absolute changes in frequency in this range (for example, decreasing from 8 to 4 Hz) equate with large *relative* changes in frequency (50% decrease) and hence tidal volume (100% increase). This in turn may reduce lung protection. Furthermore, excessive efforts to reduce Pa_{CO_2} on the basis of the lower levels found in the survivors in Mehta's study[5] may be erroneous for two reasons. First, survivors had been conventionally ventilated for a shorter period prior to initiation of HFO. Thus the lower carbon dioxide may be an epiphenomenon, reflecting less irreversible lung damage in these patients. Second, there is evidence for the lung protective aspect of hypercapnia *per se*.[11 12]

S. Moganasundram
London, UK

1 Moganasundram S, Durward A, Tibby SM, Murdoch A High frequency oscillation in adolescents. *Br J Anaesth* 2002; **88**: 708–11

2 Amato MB, Barbas CS, Medeiros DM, Magaldi RB, *et al.* Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med* 1998; **338**: 347–54

3 Offner PJ, Haenel JB, Moore EE, Biffl WI, *et al.* Complications of prone ventilation in patients with multisystem trauma with fulminant acute respiratory distress syndrome. *J Trauma* 2000; **48**: 224–8

4 Gattinoni L, Tognoni G, Pesenti A, *et al* Effect of prone positioning on the survival of patients with acute respiratory failure. *New Engl J Med* 2001; **345**. 568–73

5 Mehta S, Lapinsky SE, Hallett DC, Merker D, *et al.* Prospective trial of high-frequency oscillation in adults with acute respiratory distress syndrome. *Crit Care Med* 2001; **29**: 1360–9

6 Ferguson ND, Stewart TE. New therapies for adults with acute lung injury. High-frequency oscillatory ventilation *Crit Care Clin* 2002, **18**: 91–106

7 Cereda M, Villa F, Colombo E, Greco G, Nacoti M, Pesenti A. Closed suctioning maintains lung volume during volume-controlled mechanical ventilation. *Intensive Care Med* 2001; **27**: 648–54

8 Stenqvist O, Lindgren S, Karason S, Sondergaard S, Lundin S. Warning! Suctioning. A lung model evaluation of closed suctioning systems. *Acta Anaesthesiol Scand* 2001; **45**: 167–72

9 Piehl MA, Brown RS. Use of extreme position changes in acute respiratory failure *Crit Care Med* 1976; **4**: 13–14

10 Krishnan JA, Brower RG. High-frequency ventilation for acute lung injury and ARDS. *Chest* 2000; **118**: 795–807

11 Broccard A, Hotchkiss J, Vannay C, *et al.* Protective effects of hypercapnic acidosis on ventilator-induced lung injury *Am J Respir Crit Care Med* 2001; **164**: 802–6

12 Laffey J, Engelberts D, Kavanagh B. Buffering hypercapnic acidosis worsens acute lung injury. *Am J Respir Crit Care Med* 2000; **161**: 141–6

The output of two sevoflurane vaporizers in the presence of helium

Editor—We read with interest the short communication by Carvalho and Sanders[1] that highlights the issue of output from vaporizers for new inhalational anaesthetic agents.

A variation in performance is unsurprising when using a gas other than that for which the vaporizer has been specifically calibrated. However, a large variation in performance when using the carrier for which the vaporizer is specifically calibrated is unexpected.

Table 1 Output from Blease Datum sevoflurane vaporizer, dialled concentration 8%, fresh gas flow (air) 5 litres min^{-1}, measured by two gas analysers, Ohmeda AGM 5330 and Agilent Viridia M0126A

	AGM (% sevoflurane)	**Agilent (% sevoflurane)**
Initially	7.6	7.75
2 min	7.4	7.55
6 min	7.1	7.1
9 min	7.0	7.0
12 min	7.0	6.9
15 min	7.0	6.8
18 min	6.9–7.0	6.75
21 min	6.9–7.0	6.7
23 min	6.9	6.65
27 min	6.9	6.55
30 min	6.9	6.55

Table 2 Blease Datum sevoflurane vaporizer output with increasing carrier gas flow rates at 8% dialled concentration

Carrier gas flow (litres min^{-1})	**% Concentration (Vaporizer 1)**	**% Concentration (Vaporizer 2)**
1	8.2	8.4
3	7.9	8.4
4	7.7	8.3
5	7.5	8.2
7	6.9	7.8
9	6.7	7.3
10	6.4	6.9
12	6.2	6.2

We recently experienced a problem with the use of sevoflurane for the rapid induction of anaesthesia in a group of paediatric patients with congenital heart disease, undergoing diagnostic and interventional cardiological procedures. Patients were induced with sevoflurane at 8% dialled concentrations from one of two Blease Datum vaporizers with oxygen or air/oxygen as the carrier gas. Fresh gas flow rates between 5 and 10 litres min^{-1} were used with a Jackson-Rees modification of Ayre's T-piece and standard anaesthetic flowmeters and backbar.

After a prolonged time to loss of consciousness (several minutes), and prolonged patient struggling,[2] it was noted that maximum inspired concentration of sevoflurane achieved was 5% (measured at the patient end of the breathing system).

The backbars and vaporizers involved were tested by the hospital's department of biomedical engineering, using the Ohmeda AGM 5330 and Agilent Viridia M0126A anaesthetic gas analysers. These tests were carried out under usual operating conditions (i.e. appropriate to the clinical situation). The output from the vaporizers at a fresh gas flow of 5 litres min^{-1} and a dialled concentration of 8% with air as the carrier gas (Table 1) was measured.

The vaporizer performance was within the range specified by the manufacturer. Interestingly, however, the specified range is very wide (±20% of setting at 5 litres min^{-1} oxygen). Nielsen and colleagues[3] have documented that fewer than 30% of anaesthetists would accept a variance beyond ±10% of the dial setting

The delivery of the vaporizer decreased further at higher flows We tested the effect of increasing flows incrementally to 12 litres min^{-1} on the output of the two vaporizers, with a time of 1 min between changes and measurements. This was based on advice from the manufacturer that the time to equilibrate is less than 1 min (Table 2). The results confirm our clinical observation of decreasing output with increasing flow rate.

At a fresh gas flow of 10 litres min^{-1} (concentration setting of 8%) the specified output decreases by 1% (volume) compared with the base line at 5 litres min^{-1} Sevoflurane has a low saturated vapour pressure of 21.3 kPa at 20°C, requiring greater flow through the vaporizing chamber compared with vaporizers for other volatile agents. Previous studies have noted the lower than expected output of sevoflurane from a Sevotec 5 vaporizer at high concentrations, high flow and low fill states.[4]

The temperature compensation is known to be imprecise. A 5°C temperature drop reduces the output by approximately 0.25%, as specified in the supplier's manual (greater reduction at higher fresh gas flow rates). The combination of these errors will result in an output that may be as low as 6.5% after a few minutes of vaporizer use. There may also be a small measurement error in the analysis equipment of 0.2%.

Previous studies demonstrate that rapid induction of anaesthesia with sevoflurane at maximal initial inspired concentrations of 8% can be achieved. Mean time to loss of consciousness of 1 min 12 s was observed.[3]

Underperformance of vaporizers will lead to prolonged inhalational induction. In paediatric patients, effects such as excessive salivation, arrhythmias and laryngospasm may be observed. We feel this is an important clinical issue. Anaesthetists need to be alerted to poor performance of equipment, particularly when the variation in performance is outside the limits most would find acceptable. Manufacturers need to address such performance problems, which may be related to poor temperature compensation with a change in flow rate. Our supplier has kindly agreed to replace all the sevoflurane vaporizers in the institution with those of a more acceptable performance characteristic.

N. A. McIlree
S. Sireau
S. Jaggar
London, UK

1 Carvalho B, Sanders D. The output of two sevoflurane vaporizers in the presence of helium. *Br J Anaesth* 2002; **88**: 711–13
2 Sigston PE, Jenkins AM, Jackson EA, Sury MR, Mackersie AM, Hatch DJ. Rapid inhalation induction in children: 8% sevoflurane compared with 5% halothane. *Br J Anaesth* 1997; **78**: 362–5
3 Nielsen J, Pedersen FM, Knudsen F, Jensen MB, Ibsen M. Accuracy of 94 anaesthetic agent vaporizers in clinical use. *Br J Anaesth* 1993; **71**: 453–7
4 Seropian MA, Robins B. Smaller-than-expected sevoflurane concentrations using the Sevotec 5 vaporizer at low fill states and high fresh gas flows. *Anesth Analg* 2000, **91**. 834–6

Propofol as an antiarrhythmic

Editor—I disagree with Kannan and Sherwood's interpretation of the electrocardiograms contained in their case report.[1] They state that adenosine transiently converted a supraventricular tachycardia (SVT) to atrial flutter with a ventricular rate of 60 beats min^{-1}, which then reverted to SVT. Might I suggest that the original rhythm was atrial flutter with 2 to 1 atrioventricular block, and that the administration of adenosine simply induced a transient increase in atrioventricular block, thus unmasking the flutter waves. This response is a useful clinical test for distinguishing between atrial flutter with 2 to 1 block, which is unresponsive to adenosine, and 'true' SVT (atrioventricular nodal re-entrant tachycardia and atrioventricular re-entrant tachycardia) which is usually terminated by adenosine administration.

N. J. Morgan-Hughes
Sheffield, UK

Editor—I read with interest the case report by Kannan and Sherwood[1] who stated that administration of propofol was associated with termination of a supraventricular tachycardia (SVT). They were surprised that this effect in adults had not been reported previously in the literature. I would like to add to the discussion by reporting a case of propofol reverting a case of ventricular tachycardia (VT) to sinus rhythm.

A 76-yr-old man was admitted with shortness of breath and palpitations. He was known to have ischaemic heart disease and chronic renal impairment with secondary anaemia. He had had a DDD pacemaker inserted some years previously for first-degree heart block and left bundle branch block. His medications included amiodarone, lisinopril, isosorbide mononitrate, frusemide, bisoprolol, aspirin, and warfarin. Three days later he was transferred to the coronary care unit after an episode of VT (pacemaker not capturing), which was successfully direct current (DC) cardioverted. The following day, he again went into VT (no pacemaker capture) with associated hypotension. Preparation was made for DC cardioversion. The patient had not eaten or drunk in the preceding 8 h, which avoided the need for a rapid sequence induction. After preoxygenation, anaesthesia was induced by slow titration of propofol and after approximately 150 mg, it was noticed that the rhythm had converted to sinus (pacemaker capturing) with improvement in the arterial pressure. He remained in paced sinus rhythm for over 24 h but subsequently continued to have runs of VT that were unresponsive to medical therapy He was therefore referred for insertion of an automated implantable cardioversion device.

Kannan and Sherwood[1] have highlighted several proposed mechanisms, direct and indirect, for the action of propofol in terminating SVT. Pires and colleagues[2] examined the effects of propofol in pig hearts and concluded that propofol caused dose-related depression of the sinus node and the His–Purkinje system, but had no effect on the atrioventricular node. The exact mechanism of cardioversion in my case is unclear. Other antiarrhythmic functions of propofol are noted in a report by Miro and colleagues,[3] who described three patients with fast atrial fibrillation (AF) needing DC cardioversion. All were given propofol for sedation pre-shock and all converted to sinus rhythm after its administration.

R. M. Heames
Basingstoke, UK

Editor—Drs Kannan and Sherwood describe an interesting case of the possible conversion of a supraventricular tachycardia (SVT) to sinus rhythm by propofol.[1] They state that the 12-lead ECG on presentation (unfortunately not published in their article) was 'suggestive' of an SVT. However, the published rhythm strip (lead 11) would appear to support the alternative diagnosis of atrial flutter with 2:1 block. The failure of adenosine to convert this arrhythmia to sinus rhythm (a rare occurrence with SVT), and its apparent transient conversion to atrial flutter with 4:1 block might also support this alternative, especially when considering the predictable effect of adenosine upon AV nodal conduction. Atrial flutter may convert to sinus rhythm spontaneously, or following manoeuvres that create a Valsalva effect. Perhaps good preoxygenation with a tight fitting mask followed by cricoid pressure created these conditions? Propofol may have had some effect in converting atrial flutter in this patient to sinus rhythm but I do not think that we can be certain from the information provided by Kannan and Sherwood.

H. Hack
Manchester, UK

Editor—We would like to thank Drs Morgan-Hughes, Heames and Hack for taking an interest in our case report. We agree, in retrospect, that the original rhythm in our patient was atrial flutter with an atrioventricular conduction block. A definitive diagnosis before the administration of adenosine was hindered by the varying ventricular rates. Hence, we had used the term 'rhythm suggestive of supra ventricular tachycardia (SVT)' in our case report description. Although adenosine unmasks atrial flutter by prolonging atrioventricular nodal conduction, it can rarely induce atrial flutter in patients with paroxysmal SVT and *vice versa.*[4 5] Since it is less likely that a given patient would have two different types of supraventricular arrhythmias at different points in time, a more appropriate title would have been 'Termination of atrial flutter by propofol'. Interestingly, atrial flutter has been classified as a form of SVT.[6] In spite of what we thought was an extensive search of the literature, we failed to identify the reported cases of termination of atrial fibrillation with propofol.[3] We would like to thank Dr Heames for bringing them to our attention. His report of termination of ventricular tachycardia with propofol is interesting. It is not clear which anaesthetic the patient received for the first cardioversion. If the patient had received propofol for the same, it obviously did not terminate the rhythm at that instance. As for its effect on atrioventricular node conduction, Alphin and colleagues[7] have demonstrated that propofol slows atrioventricular conduction time in a concentration-dependent manner in guinea-pigs.

S. Kannan
N. Sherwood
Birmingham, UK

1 Kannan S, Sherwood N. Termination of supraventricular tachycardia by propofol. *Br J Anaesth* 2002; **88**. 874–5
2 Pires LA, Huang SK, Wagshal AB, Kulkarni RS. Electrophysiological effects of propofol on the normal cardiac conduction system. *Cardiology* 1996, **87**: 319–24
3 Miro O, de la Red G, Fontanelo J. Cessation of paroxysmal atrial fibrillation during acute intravenous propofol administration. *Anesthesiology* 2000; **92**. 910
4 Strickberger SA, Man KC, Daoud EG, *et al.* Adenosine induced atrial arrhythmia· a prospective analysis. *Ann Intern Med* 1997; **127**: 417–22
5 Slade K, Garratt CJ. Proarrhythmic effect of adenosine in a patient with atrial flutter. *Br Heart J* 1993; **70**: 91–2
6 Morillo CA, Pava F. Supraventricular tachycardia. In: Crawford MH, DiMarco JP, eds. *Cardiology*. London: Mosby, 2001, Section 4, 9.3
7 Alphin RS, Martens JR, Dennis DM. Frequency dependent effects of propofol on atrioventricular nodal conduction in guinea pig isolated heart. Mechanism and potential antidysrhythmic properties. *Anesthesiology* 1995; **83**: 382–94

Successful defibrillation in the prone position

Editor—We read Miranda and Newton's[1] case report of 'Successful defibrillation in the prone position' with interest. We wish to add some important recommendations to those made in the discussion. As the authors emphasize, the primary objective for the treatment of ventricular fibrillation (VF) is early defibrillation. The probability of successful defibrillation and subsequent survival to hospital discharge is inversely related to the time interval between onset of VF and delivery of the first shock.[2] When ventricular fibrillation occurs in the prone position, whether in the operating theatre or the intensive care unit, there are both theoretical concerns and practical strategies that may improve the success of defibrillation therapy, if applied clinically.

Defibrillation is accomplished by passage of sufficient electric current (amperes) through the heart. The energy chosen (joules) and the transthoracic impedance (ohms), or resistance to current flow, determine the current flow. Factors that determine transthoracic impedance include energy selected, electrode size, paddle–skin coupling material, number of and time interval between previous shocks, phase of ventilation, distance between electrodes (size of the chest), and paddle electrode pressure.[2]

In theory, electrode pads (or paddles) should be positioned to minimize transthoracic impedance and incorporate as much of the fibrillating myocardium between the defibrillating electrodes as possible. This was the rationale used by Lown[3] to advocate the anterior–posterior positions for transthoracic cardioversion of atrial fibrillation. Thus, a critical mass of myocardium is more likely to be defibrillated. In the prone position the heart is displaced anteriorly, and positioning electrodes in the left posterior axilla and below the right scapula may not provide an adequate vector for shock delivery. Furthermore, the transthoracic impedance will be greatly increased, especially during positive pressure ventilation with positive end-expiratory pressure.

Whilst the prone patient is not easily moved to the supine position, especially in the neurosurgical setting, it may be relatively simple to manoeuvre the patient sufficiently to allow application of electrode pads (as opposed to defibrillator paddles) to the standard apical and right infraclavicular regions. This will allow a shock to be delivered across a more appropriate vector. If this is not possible, defibrillation with an impedance compensating device (now commonplace in cardiology departments), which delivers a truncated exponential biphasic shock, would be the best option for the suboptimal prone position. Indeed, even in the out-of-hospital cardiac arrest scenario, Schneider and colleagues[4] demonstrated three sequential 150 J shocks to be 98% successful in electrical cardioversion of VF using standard electrode positioning with an impedance compensated, biphasic waveform (96% were successfully defibrillated with the first shock). Defibrillation should be carried out in expiration without positive end-expiratory pressure, to further minimize transthoracic impedance. We propose that consideration should be given to the use of these strategies and also to the availability, in close proximity to prone patients, of both electrode pads in addition to standard defibrillation paddles and the modern generation of impedance-compensating defibrillators. It may also be prudent to attach electrode pads to intensive care patients, who are at a high risk of ventricular arrhythmias, before turning them prone. The eventual strategy employed by the attending physician for the treatment of VF in the prone position will be a balance between the time taken to achieve optimal defibrillation and the concerns discussed above.

S. J. Walsh
A. Bedi
Belfast, UK

Editor—Thank you for the opportunity to reply to Bedi and Walsh. They propose several strategies which may improve the chances of successful defibrillation in the prone position. We agree that, in the prone position, electrode pads may be easier to apply than defibrillator paddles to the standard apical and right infraclavicular regions. In the situation we described, however, electrode pads were not available. We also agree that the timing of defibrillation in relation to respiration, as well as the use of impedance compensating devices, would improve the chances of successful defibrillation by reducing thoracic impedance.

C. Miranda
London, UK

1 Miranda CC, Newton MC. Successful defibrillation in the prone position *Br J Anaesth* 2001; **87**: 937–8

2 ECC Guidelines: Part 6: Advanced Cardiovascular Life Support. Section 2: Defibrillation *Circulation* 2000; **102** [Suppl I]: I-86–I-89

3 Lown B Electrical reversion of cardiac arrhythmias. *Br Heart J* 1967; **29**: 469–89

4 Schneider T, Martens PR, Hans P, *et al.* Multicenter, randomized, controlled trial of 150-J biphasic shocks compared with 200- to 360-J monophasic shocks in the resuscitation of out-of-hospital cardiac arrest victims. *Circulation* 2000; **102**: 1780–7

Pencil point spinal needles and neurological damage

Editor—The editorial by Fettes and Wildsmith[1] discusses the important issue of neurological damage after spinal anaesthesia with pencil point needles. They mention several factors about these needles and how these may predispose to neurological damage. I would like to comment on three of the four points they make in the section on equipment.

Their first point is that pencil point needles require to be inserted for a greater length because the needle orifice is situated approximately 1 mm proximal from the tip. Whilst the latter is true, there is no evidence of the former. We performed a pilot trial, which did not support this point (see below).

Their third point was that pencil point needles may require a slightly greater force to advance and that this may predispose to 'overshoot' and risk neurological damage. An *in vitro* study comparing 25 gauge Becton Dickinson Whitacre and Quincke spinal needles, showed that a threefold increase in force (0.12 kg) was required to puncture bovine dura mater with the former compared to the latter (0.04 kg).[2] It would be logical to presume that greater force is required to advance pencil point needles through the other tissues in the back. The risk of 'overshoot' depends on how the force is applied; if it is applied in a controlled manner, there should be no overshoot.

Their fourth point concerned 'tenting' of the dura. Tenting of the dura does occur before puncture. Spinaloscopy in a system open to atmospheric pressure (cadaver dissection) has shown that the dura 'tents' and then retracts to its original position after needle puncture. This occurs with both types of needle tip but is more pronounced with a pencil point tip.[3] The normal practice of spinal anaesthesia, however, occurs in a system which is 'closed' to atmospheric pressure.

We studied epidural pressures and distance to dural puncture in patients undergoing subarachnoid anaesthesia performed either with a Whitacre (pencil point) 25G or Quincke 25G spinal needle [4] The subarachnoid depth and dural tenting was similar in both groups, implying that a Whitacre needle is not inserted closer to the spinal cord. However, the median (95% CI) pressure recorded just prior to dural puncture was significantly more negative in the Whitacre group (–32 (–52 to –10 mm Hg) *vs* –2.5 (–10 to 5.5 mm Hg, $P<0.02$ in the Quincke group)). The higher pressure gradient would favour retraction of the dura back to its original position even more than in the 'open' system. This would obviate the need to advance the needle further to ensure the orifice is entirely within the subarachnoid space.

The production of a greater negative epidural pressure with the Whitacre needle generates the higher force required to puncture the dura and also limits the distance of tenting, which therefore limits the distance of the needle to the neural tissue. This would not be the situation in an 'open' system, such as the needle through the needle combined spinal epidural technique, where the negative pressure would not be generated.

Our study involved only a small number of patients and we were only able to measure distances as small as 0.5 mm.[4] However, we concluded that in a 'closed' spinal anaesthetic technique, there is no evidence that pencil point needles require to be inserted any further than Quincke needles. Therefore they should not predispose to any increased contact with the neural tissues.

M. G Serpell
Glasgow, UK

Editor—We thank Dr Serpell for his interest in our editorial.[1] Much of the editorial was based on first principle analysis; data are always to be preferred if they are available, but those data must be accurate.

Dr Serpell disagrees with our view that it is necessary to insert more of a 'pencil' point needle into the subarachnoid space than a standard Quincke point, the basis for this being a study with 'a small number of patients', published only in abstract form 5 yr ago.[4] Reviewing that abstract, we found that changes in the pressure recorded from the needle as it was advanced through the ligaments were used to identify key anatomical landmarks (e.g. the point of moving from the ligamentum flavum into the epidural space). The length of needle remaining outside the patient was measured at each stage by some unidentified method. This strikes us as a less than reliable technique because it makes assumptions about the meaning of the pressure changes recorded as the needle moves forward, and appears to take no account of skin 'tethering' as it does so. Dr Serpell admits to being able to measure distances no smaller than 0.5 mm, and we wonder about even that accuracy given the methodology. In addition, it is important to recognize that the side port of the Whitacre needle will mean that approximately 1 mm of needle will be inserted into each space before a pressure change is observed (whereas it will be much less than this with the Quincke needle). Perhaps confirming our concerns about the method, the data presented in the abstract are for only 10 out of 16 'Whitacre', and 9 out of 12 'Quincke' patients because of inability to identify two out of the four key landmarks.

The actual measurement of epidural pressure is more straightforward, and we note that Serpell[4] found a statistically significantly greater decrease in pressure as the Whitacre needle was advanced. It is now well recognized that much of the negative pressure identified in the epidural space is due to dural tenting as the needle is advanced,[5] so a greater decrease in pressure would, to us, suggest that the needle has been inserted further, even before the dura has been breached. Serpell's analysis of the differences in the dynamics of pressure change with the two different needles is not sustainable given the problems with the measurement of distance.

Finally, we are grateful to Dr Serpell for providing additional evidence that the force needed to insert a 'pencil' point needle is greater.[2 4] He argues that the risk of overshoot depends on how well controlled is the force used to insert the needle, but the real issue is that the greater the force needed, the greater the risk of overshoot, especially in inexperienced hands. That is one of our main concerns.

P. D. W. Fettes
J. A. W. Wildsmith
Dundee, UK

1 Fettes PDW, Wildsmith JAW Somebody else's nervous system *Br J Anaesth* 2002; **88**: 760–3

2 Westbrook JL, Uncles DR, Todd Sitzman B, Carrie LES. Comparison of the force required for dural puncture with different spinal needles and subsequent leakage of cerebrospinal fluid *Anesth Analg* 1994, **79**· 769–72

3 Mollmann M. Dural trauma, audiovisual presentation Presented on September 9, 1993 at the 12th Annual European Society for Regional Anaesthesia, Dublin, Ireland

4 Anderson L, Marshall S, Brydon C, Serpell MG Comparison of dural indenting between Whitacre and Quincke tipped spinal needles *Br J Anaesth* 1997, **78**. 468–9P

5 Aitkenhead AR, Hothersall AP, Gilmour DG, Ledingham IM Dural dimpling in the dog. *Anaesthesia* 1979, **34**· 14–19

British Journal of Anaesthesia 89 (5): 802–5 (2002)

Book Reviews

Pulse Oximetry, 2nd Edn. J. T. B. Moyle. Published by BMJ Books, London. Pp. 182; indexed; illustrated Price £19.95. ISBN 0-7279-1740-4.

This publication reviews in 12 chapters, the history, technical aspects, clinical applications, and limitations of pulse oximetry. This second edition contains a new chapter, on pulse oximetry at high altitude, that includes its use during aircraft flying.

The books gets off to a 'bumpy' start. In the very first sentence, the name of the town where Lambert published his description of the relationship between the absorption of light and the amount of absorbent is misspelled as 'Augsberg' instead of 'Augsburg'. Admittedly, except for this reviewer who happens to be German, who actually cares? But how about the following sentence? It lists 1853 as the year of birth of August Beer, and then lists 1851—two years before his birth—as the year in which Beer published findings that are now known as the 'Beer–Lambert law'. The simple explanation for the obvious error is that Beer did not live (as listed) from 1853–1932, but from 1825–1863. One wonders how this could possibly have escaped editorial scrutiny. After such 'preconditioning', I was prepared for the worst. However, very rapidly it became apparent that, if anything, a characteristic of this book is its lack of errors. On a personal note, this is one of the rare publications where German language references are quoted without the usual numerous misspellings.

The first chapter deals very briefly with the history of pulse oximetry. The following chapters on 'Optical principles' and on 'How pulse oximetry works' are very informative, to the point, and of clinical relevance. The latter chapter includes a description of methods used to eliminate artefacts, and of the use of pulse oximetry with the magnetic resonance imaging scanner. We are reminded that many pulse oximeters calculate the ratio of the amplitude of the components of red and infrared signals and apply it to a table that relates this ratio to a specific oxygen saturation value, resulting in Sp_{O_2}. Those who are particularly interested in the historical or technical aspects of pulse oximetry might well regard the depth of coverage of this topic as inadequate.

The chapter on 'Calibration' emphasizes that pulse oximetry indicates a value, referred to as Sp_{O_2}, that is best described as 'oxygen saturation as measured by pulse oximetry'. Problems associated with the need for *in vivo* calibration, and attempts at producing devices that allow *in vitro* calibration are discussed. The importance of the plethysmogram is underlined by the chapter on 'Photoplethysmography' 'Physiology of oxygen transport' is a concise review of the subject. It is followed by 'Pulse oximetry at high altitude', which provides interesting information of clinical relevance.

The main emphasis of the book is clearly placed on the general and specific clinical applications of pulse oximetry. The chapter on 'General clinical applications' starts with the statement that 'the clinical applications of pulse oximetry in medicine are as important as oxygen to life', and finishes with '...pulse oximetry should form part of any clinical investigation where there is the remotest risk of hypoxaemia'. Although these may seem like overstatements, the author's opinion is based on numerous findings that hypoxaemic episodes are frequently precursors of pathological events.

I have mixed feelings about the chapter on 'Specific clinical applications', the most extensive of all (49 pages, 126 references). It lists numerous areas where pulse oximetry has been applied (emergency medicine, anaesthesia, postoperative recovery, endoscopy, dentistry and oral surgery, sleep apnoea, neonatology). On the one hand, it provides some important messages, such as 'It cannot be emphasised enough that pulse oximetry can be safely used only if the limitations of the technique are realized by all users'. The discussion on why Sp_{O_2} often correlates poorly with Pa_{O_2} in the plasma of newborns is very useful and clinically relevant. On the other hand, the descriptions of aetiology, pathology, anatomy, and even treatment of various conditions are (in this context) excessively detailed and out of context. I doubt that those who buy a book entitled 'Pulse oximetry' are particularly interested in information that is more appropriate in medical texts. All in all, this chapter makes for somewhat tedious reading.

The chapter on 'Limitations and morbidity' contains interesting information, but has itself some limitations. The value of the statement that 'physiological dyes...when administered intravenously as a bolus, cause inaccuracy in Sp_{O_2} readings' is limited because the type of inaccuracy (i.e. over- or underestimation) is not detailed. Similarly, it is stated that some pulse oximeters show a slower response time than others, but actual values are not listed. Although indirectly implied, I missed a clear statement that the pulse oximeter will report 100% saturation, whether the Pa_{O_2} is 150, 300 or 600 mm Hg.

In the chapter on 'Dyshaemoglobins' we are reminded that conventional pulse oximeters are calibrated only for adult haemoglobin. The discussion on the effect of carboxyhaemoglobin on pulse oximetry is useful and informative. The author's statement that 'Pulse oximetry should never be used with patients who are known to have inhaled carbon monoxide or been involved in any conflagration' might be considered somewhat extreme. I would have been interested in any possible effect of haemoglobin replacement solution on pulse oximetry. The book finishes with a brief chapter on 'Fetal pulse oximetry'.

Is this publication up-to-date? The revised first edition was published in 1998. Of approximately 320 references, a mere 40 (13%) have been published since 1996. It is noteworthy that in the largest chapter on the specific clinical applications of pulse oximetry with a total of 126 references, the latest publications (and there are only two) are from 1997. Does this imply that most has been said on this topic and that there is no longer any progress in this area?

For anaesthetists and intensivists, statements like 'Normal oxygen saturation as indicated by any oximeter does not necessarily rule out hyperventilation' (p 81), seem trivial. I doubt that many are prepared to follow the recommendation that 'during the acute phase of an exacerbation (of chronic obstructive pulmonary disease, personal comment) it may be necessary to infuse a respiratory stimulant such as doxapram intravenously as a form of respiratory drive' (p.84). For an anaesthetist, it is surprising that two large, randomized evaluations of pulse oximetry in more than 20 000 patients[1 2] have not been mentioned in a publication on pulse oximetry.

When I was introduced to pulse oximetry, I remember the initial difficulties in memorizing the correlation between oxygen saturation and Pa_{O_2} values. What a help it was when I learned about the '30/30' rule(s) of thumb, which state(s) that saturation values of 90, 85 and 80% correspond roughly to Pa_{O_2} values of 60, 55 and 50 mm Hg respectively, and a saturation value of 30% corresponds roughly to a Pa_{O_2} of 30 mm Hg. I have missed this very useful practical advice in this publication.

These are all minor criticisms that do not distract from the overall value of this publication. All in all, it is well written,

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

provides clinically useful information, and I enjoyed reading it. It represents reasonable value for money. Nevertheless, I think that this is a publication for a departmental library rather than for individual purchase.

H.-J. Priebe
Freiburg, Germany

1 Moller JT, Pendersen T, Rasmussen LS, *et al.* Randomized evaluation of pulse oximetry in 20,802 patients: I. Design, demography, pulse oximetry failure rate, and overall complication rate. *Anesthesiology* 1993; **78**: 436–44

2 Moller JT, Johannessen NW, Espersen K, *et al.* Randomized evaluation of pulse oximetry in 20,802 patients: II. Perioperative events and postoperative complications. *Anesthesiology* 1993; **78**: 445–53

Anaesthesia for the High Risk Patient. I. McConachie (editor). Published by Greenwich Medical Media, London. Pp. 265; indexed. Price £22.50. ISBN 1-84110-072-2.

Anaesthesia for the High Risk Patient is a small volume that is edited by I. McConachie from the Blackpool Victoria Hospital, UK with contributions from his anaesthetic colleagues, and from cardiologists and the acute pain service in Blackpool.

The book is aimed at a wide readership of anaesthetists (both trainees and consultants), surgeons and intensivists who may be involved in the management of the high-risk patient. The book aims to provide practical advice on the management of such patients presenting for surgery It is supported by background information and references to enable the reader to understand the evidence base behind the advice on the assessment, anaesthetic and perioperative management of these patients.

The information is grouped into 17 chapters covering a wide variety of areas such as: identification of high-risk patients and the scoring systems used to assess them; lessons to be learnt from the NCEPOD reports; problems with elderly patients; and problems with patients with underlying cardiac, renal or respiratory disease. There are chapters on admission criteria to intensive care and high-dependency units, as well as the management of patients for emergency aortic aneurysm surgery.

The advice given is backed up with references from both anaesthetic and surgical journals as well as extracts from reports produced by the Royal Colleges. Much of the information is current, with some of the references coming from work published as recently as 2001. There are also references made to Department of Health publications such as the National Service Framework for Coronary Heart Disease. Each chapter contains suggestions for further reading which point the reader to definitive articles in the literature on subjects covered in the chapters. There are also references highlighting controversies within certain subjects.

Some of the advice given may be seen as controversial, such as the suggestion of using ketamine in shocked patients and the use of remifentanil for laparotomies. But references are given to support the arguments. There are points that put to rest some myths held by surgeons, such as that neostigmine can cause anastomotic breakdown in patients undergoing bowel surgery. However, the surgical factors that may cause anastomotic breakdown are clearly listed. Much of the information given is both useful and relevant such as the morbidity and mortality figures for patients with various conditions. Such data enable one to discuss the risks and benefits of surgery with both surgeons and patients, or patients' relatives.

The information is easily accessible, being presented in a readable and concise style with the use of headings and bullet points throughout. The information in the chapters follows a logical sequence with practical advice followed by background information.

In summary, this is an interesting and useful book that will appeal to a wide readership. The information contained will make it a useful reference for both consultants and trainees involved in the management of high-risk patients It will also make a useful revision aid, covering high-risk patient management for candidates sitting the Fellowship examination.

J. M. King
Stoke-on-Trent, UK

Spinal Cord Injury Pain: Assessment, Mechanisms, and Management. R. P. Yersierski and K. J. Burchiel (editors). Published by IASP Press, Seattle. Pp. 443; indexed; illustrated Price $89 (IASP members $67). ISBN 0-931092-43-4

This International Association for the Study of Pain (IASP) publication represents another volume in the series 'Progress in Pain Research and Management' which brings into the focus the problem of chronic neuropathic pain after spinal cord injury (SCI). It used to be regarded as a clinical entity suitable for psychiatric referrals, and contributors state at various points that there has been little therapeutic advance in this realm in the last 50 yr. Stimulated by their awareness of this, IASP had formed a task force in 1997 resulting in the 3rd Research Symposium in 2001, which is crystallized in the present volume. There are 46 contributors from the USA, eight from Scandinavia and Dr Siddall from Sydney, Australia. All bar two chapters draw directly on work on SCI and four chapters present work not previously published.

The mood conveyed is now one of greater optimism for the future; there is even talk of genetically engineered cellular delivery systems which may allow the chronic pain of SCI to be one of its first curable dysfunctions. However, such a statement taken out of context belies the complexity of SCI pain, which together with its unpredictability has bedevilled systematic progress in research and treatment and no adequately sized controlled clinical trials have been published.

Clinical characteristics and assessment are covered in Part I in 82 pages, with a particular focus in Chapter 1 on the need for an internationally agreed taxonomy. In tier one of this classification there is a broad grouping of pain into nociceptive and neuropathic pain. Tier two comprehends 'above-level', 'at-level' and 'below-level' pain within the latter category, whilst the more easily managed musculoskeletal and visceral pain are in place in the former category. The latter, although common in SCI, are not explored further in the book. Tier two is subdivided into tier three for specific structures and pathology.

Strengths and weaknesses of the 28 already published classifications of SCI pain are reviewed in the second chapter, which endorses the proposed new taxonomy if combined with full psychometric and psychosocial evaluation.

The second part in 176 pages covers experimental work with data from both animal and human studies. Findings generally confirm that a principle condition for the development of central 'below-level' pain is the interruption of the spinothalamic tracts bearing thermal and normal pain sensations, but the role of dorsal column sensory input in neuropathic pain is less clear. Loss of grey matter is likely to be important in addition to loss of white matter and sprouting from Rexed lamina I into II is evident after transection. More centrally, microelectrode studies in a small number of SCI patients during ablation of the thalamus' principle sensory nucleus, the ventral caudal nucleus, show a number of changes when compared with patients being treated for movement disorders. Changes demonstrable cortically at the level of the cingulate gurus and insula may serve to perpetuate established pain. The third section on 'Imaging' concludes with work on the operative treatment of painful syringomyelia with fetal spinal cord graft tissue. It was found that any reduction in pain could usually be related to the cyst regression on follow-up imaging, but the technique is demanding, considering the total extent of the syrinx in some cases.

The fourth part has seven chapters devoted to treatment, with an excellent introduction by Haythornthwaite and Wegener on the difficulties of SCI pain trials. Apart from the factors already discussed above, additional constraints arise from. limitations in mobility; long travel distances; tendency for exacerbations to occur prior to initial consultations; the unreliablility of a lidocaine infusion as a predictor; whether or not to dichotomize the outcome, for instance more or less than 50% pain relief; and inclusion in some past studies of patients with low initial pain levels. Their recommendations are for multiple baseline assessments, use of active placebos consistently, multiple measures of outcome, an intention to treat analysis and the need for multicentre trials to achieve the 500 patients required in each treatment group.

There follows a review by Finnerup of the ten pharmacological trials which fulfil the criteria of being randomized, double-blind, and placebo-controlled, though no trial has more than 30 patients, and only half of these trials concerned oral agents. Trazodone was the only representative in the antidepressant category and no oral therapy with the possible exception of lamotrigine has been shown to be effective. The presentation of the results of a pilot study of topiramate by Harden, however, are encouraging and the longitudinal studies of the success of gabapentin as part of combination therapy also merit further study. The final chapter in this section reviews the technique, benefits and complications of dorsal root entry zone coagulation, stressing the lack of effect of cordotomy of the spinal thalamic tracts

The final chapter by the editors entitled Future Directions emphasizes the need for a multi-disciplinary and multi-component approach, and urges more longitudinal studies as well as multicentre studies based upon agreed taxonomy. The scientific investigations also need to look at why some with SCI do not suffer pain, and future success in regenerative techniques for motor recovery will be blighted if it is accompanied by neuropathic pain.

The book is an essential read for specialists in spinal cord care, for pain specialists in tertiary pain centres who may occasionally treat patients with SCI and for anyone who is interested in the fundamental mechanisms of neuropathic pain.

J. W. H. Watt
Southport, UK

How to Survive in Anaesthesia, 2nd Edn. N Robinson and G. Hall. Published by BMJ Books, London. Pp. 191; indexed. Price £22.50. ISBN 0-7279-1683-1.

First, read the preface: 'If you are a trained anaesthetist, you should not be reading this.' So I did not, or at least I gave it first to one of our senior house officers, about to move to a specialist registrar post. She was complimentary and wrote thus:

> The first few months whizzed by in a blur of unfamiliar bleeping machines, alien numeric displays, and small multicoloured sticky labels on syringes which all looked the same except for the large milky one. When time was up and the reality of 'going solo' arrived, it was all a bit of a shock. Would I remember which was more appropriate: vecuronium or atracurium? Should I give midazolam at induction of anaesthesia? What was the correct gas flow setting for a circle system? Suddenly I wished I'd paid more attention in the previous few months.'
>
> *How to Survive in Anaesthesia* is written exactly for that sort of person: the trainee anaesthetist embarking on that first year of anaesthesia. It does not deal with the finer points of anaesthesia and steers clear of confusing controversies (the nitrous/air debate is well and truly off limits), but it explains clearly the simple essential principles of safe anaesthesia
>
> There are three sections. The first covers the necessary preparation of oneself, the patient, and the anaesthetic machine and equipment. The second section covers emergencies, including a well-structured chapter on haemorrhage and transfusion, as well as chapters on less common problems The third section—'Passing the gas'—has separate chapters for the different surgical specialties, and covers all major types of surgery found in most district general hospitals. It explains the more common operations, their associated complications, and any anaesthetic modifications that may be expected or required. There are plenty of boxes highlighting important information.
>
> This book is definitely written by anaesthetists doing the job. It reads almost as if your consultant is there chatting you through the case—which is reassuring when you are about to face (or are in the middle of) a new and daunting situation. Although many of the topics are extremely serious (when is anaphylaxis ever funny?), the authors manage to use humour and to make it entertaining without losing sight of the important principles. It certainly achieves its aim: 'to provide a concise readable text that will introduce the new trainee in anaesthesia to safe clinical practice', and you cannot argue with that, when the book manages to explain diffusion hypoxia in just three sentences comprising in total 55 words.

Our senior house officer would have found the book helpful: would I have recommended it to her? Unequivocally yes. It is short, snappy and sensible. This is a second edition, and I hope it makes a third. It could be improved. The external jugular vein deserves mention as occasionally life-saving. The authors are explicitly not trying to teach basic science, but give the equations of soda-lime, yet gloss simplistically over the fresh gas requirements of rebreathing systems. Surely, monitoring the concentration of a volatile agent is now routine rather than specialized? While I agree that airway obstruction must always be excluded whenever there is low oxygen saturation, the commonest cause of a pulse oximetry alarm is that the probe has slipped off the finger. Mention is needed of the 'twitchy' appearance of patients whose neuromuscular block is not fully reversed.

The writing is direct and no-nonsense, but the authors are too fond of the vogue word 'mandatory'. Senior house officers do need telling what must be done, but the better word is essential or (as in italics on p. 43) imperative. It is imperative that airway pressures be monitored during mechanical ventilation, but it is mandatory—required by law—that operative deaths are reported to the coroner. Which brings me to the book's only major omission: advice on how to handle disasters, especially death on the operating table. If not given support, trainee anaesthetists can be destroyed by this.

S. Pickard and N. W Goodman
Bristol, UK

Notable Names in Anaesthesia. J. Roger Maltby (editor). Published by The Royal Society of Medicine Press Ltd, London. Pp. 254; indexed; illustrated. Price £19.50. ISBN 1-85315-512-8.

The editor recalls in his preface that as a medical student he and his colleagues were often asked for more detail if they mentioned an eponym (e.g. Langenbeck, Trendelenburg), and no doubt many of us had similar experience. In Maltby's case, the interest persisted Many years later, looking up Bailey and Bishop's *Notable Names in Medicine* he found that there were no eponymous anaesthetists, and he has tried to fill the void.

There are 76 short portraits, usually three or four pages long, accompanied by passport-type photographs of the subjects and three recommendations for further reading. Names such as Magill, Hartmann, Sellick and Bier that anaesthetists may use daily are all there, together with those who invented equipment or techniques or are associated with major advances. Some of course are not anaesthetists (Bier, Esmarch, Mapleson). More than a dozen of the subjects have written their own accounts, and there are a few others who have supplied information, but otherwise the editor has written the chapters himself.

He has not discussed the question of what it is that separates the inventive personality from the everyday practitioner, but most of the names were solving problems, seeking improvements, applying the fruits of research, or even following up an idea from conversation. Virginia Apgar's scoring system arose from a breakfast discussion with medical students. The stimulus for the development of Rubens' valve and self-inflating bag was a Danish truck-drivers' strike which threatened the supply of oxygen. In some cases, there is evidence of determination in overcoming obstacles to qualification in medicine. The English pioneer John Snow walked 200 miles from York to London to enrol at the Hunterian School of Medicine. Bonica's father died when he was young, and Bonica earned money as a professional wrestler to pay his way through medical school. Waters supplemented his income by working as a hospital orderly, which the editor suggests may have informed his common sense attitude. By contrast, Kaye in Australia had private means which enabled him to work full-time in anaesthesia.

Some of the subjects here, not unlike the scientific polymaths of the seventeenth to the nineteenth centuries, could boast achievements in other fields. Brain had an Oxford degree in modern languages and literature before moving to science, and Fink could speak seven languages. Both Apgar and Guedel were gifted musicians of professional standard, the latter despite losing three fingers of his right hand in an accident at the age of 13 yr. Bier planted 750 hectares of mixed forest at Sauen in Germany which is now a place of pilgrimage for ecologists.

Those are only a few examples of the interesting details in the lives of exceptional people Inevitably, some are of larger significance than others, and some will be less known on one or other side of the Atlantic Ocean. The editor expects disagreement on the selections and omissions Although he has nothing named after him, it is a bit disappointing that Ibsen and the polio epidemic of 1952 are not mentioned. This demonstrated the therapeutic possibilities of long-term artificial ventilation of the lungs, and was the start of the pathway to the intensive therapy unit.

Although the editor does not claim to have written a history of anaesthesia, the book of course is packed with historical information. It is imaginative in concept and successful in execution. Buy it, dip into it, and enjoy it.

P. M. E. Drury
Liverpool, UK

Guide to Contributors

The purpose of the *British Journal of Anaesthesia* is the publication of original work in all branches of anaesthesia, including the application of basic sciences. One issue each year deals mainly with material of postgraduate educational value.

Papers for publication and all editorial communications should be addressed to: Professor J. M. Hunter, Editor-in-Chief, *British Journal of Anaesthesia*, University Department of Anaesthesia, Royal Liverpool University Hospital, The Duncan Building, Daulby Street, Liverpool L69 3GA, UK. Tel./Fax: +44 (0) 151 706 4005. E-mail: bja@liv.ac.uk

Papers

Papers submitted must not have been published in whole or in part in any other journal, and are subject to editorial revision. It is a condition of acceptance for publication that copyright becomes vested in the journal and permission to republish must be obtained from the publisher.

Papers based on clinical investigation should conform to ethical standards as set out in the Declaration of Helsinki and should normally include a statement of approval from an appropriate Ethics Committee. In the case of animal studies it is the responsibility of the author to satisfy the Board that no unnecessary suffering has been inflicted. Studies from the UK should specify the Home Office Licence number; from elsewhere, a statement of approval from an appropriate licensing authority.

Legal considerations

Authors should avoid the use of names, initials and hospital numbers which might lead to recognition of a patient. A patient must not be recognizable in photographs unless written consent of the subject has been obtained. A table or illustration that has been published elsewhere should be accompanied by a statement that permission for reproduction has been obtained from the authors and publishers.

Preparation of manuscript

Four copies of each manuscript (including revised texts) should be submitted and should indicate the title of the paper, the name(s), full address(es) of the author(s), and be in letter quality heavy type (not dot matrix), double-spaced on one side only of the paper, with a wide margin. Contributors should retain a copy in order to check proofs and in case of loss. Where possible, manuscripts should also be submitted on disk. Our preferred format is a 3.5″ PC floppy disk with the file written in Word 6 for Windows. However, it is also possible to process disks submitted in other formats, provided sufficient information is supplied to enable conversion to the preferred format. Articles on disk should be prepared in the simplest possible form. Please do not use endnotes, footnotes, etc. for references. Correct fonts, type sizes, column measures, etc, will be added by the technical editor.

Each of the four copies submitted must be accompanied by a complete set of figures. One set of figures must be unmounted glossy prints (see below); the three other sets may be photocopies.

Manuscripts should be accompanied by a formal letter of request for publication which should be signed by all the authors. There should be a clear declaration of any financial or commercial interest which any author may have in the material. The Editor may wish to see raw data if necessary.

Papers in recent issues of *British Journal of Anaesthesia* should be consulted for general and detailed presentation. They are most often subdivided into:

- Title page
- Summary, including Keywords
- Introduction (not headed)
- Methods
- Results
- Discussion
- Acknowledgements
- List of references
- Tables (including legends to tables)
- Illustrations (including captions)

Title page

There should be a separate title page, including the name(s) and address(es) of all author(s). It should be made clear which address relates to which author. Authors' present addresses differing from those at which the work was carried out, or special instructions concerning the address for correspondence, should be given and referenced at the appropriate place in the author list by superscript numbers. If the address to which proofs should be sent is not that of the first-mentioned author, clear instructions should be given in a covering note and not on the title page. The title page should be paginated as page 1 of the paper.

A short running title containing not more than 50 characters and spacing should be included.

Summary

The summary will be printed at the beginning of the paper. It should be on a separate sheet, in structured format (Background; Methods; Results; and Conclusions) for all original articles (Clinical Investigations, Laboratory

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Investigations, and Short Communications) but not for Reviews, Case Reports, or Commentaries. It should give a succinct account of the problem, in up to 250 words. It may be used as it stands by abstracting journals. References are not used in this section, except in exceptional circumstances.

Three to five key words or phrases (for indexing) should be included below the summary.

Introduction

The introduction should give a concise account of the background of the problem and the object of the investigation. Previous work should be quoted only if it has a direct bearing on the present problem.

Methods

Methods must be described in sufficient detail to allow the investigation to be interpreted and repeated by the reader. Any modification of previously published methods should be described and the reference given. If the methods are commonly used, only a reference to the original source is required.

Drugs

When a drug is first mentioned it should be given the international non-proprietary name, followed in parentheses by the chemical formula only if the structure is not well known, and by the capitalized proprietary name.

Results

Description of results, while concise, should permit repetition of the investigation by others. Data should not be repeated unnecessarily in text, tables and figures, and unwarranted numbers of digits should be avoided. Significance should be given as values of probability.

Discussion

The discussion should not merely recapitulate the results, but should present their interpretation against the background of existing knowledge. It should include a statement of any assumptions on which conclusions are based.

Acknowledgements

Acknowledgements will be printed in small type. They should be brief, and should include reference to sources of support and sources of drugs not freely available commercially. Individuals named must be given the opportunity to read the paper and approve their inclusion in the acknowledgements, before the paper is submitted.

References

There should be a list of references at the conclusion of the paper, commencing on a new sheet.

References must be numbered consecutively in the order in which they are first mentioned in the text, with the exception of review articles, when references should be arranged alphabetically.

References in text, tables and legend should be identified by arabic numbers appearing in the text in superscript, for example ^{5} or $^{5-7}$ or $^{5\ 16}$ for unrelated references. When a table or figure is first mentioned, its reference must continue the sequence.

Use the style of references adopted by the US National Library of Medicine and used in *Index Medicus.* The titles of journals should be abbreviated.

The names and initials of more than six authors should be abbreviated to three authors followed by *et al.*

Text references to 'unpublished observations' or 'personal communications' should not be included in the final list of references. Authors are responsible for verifying that the wording of references to unpublished work is approved by the persons concerned. Papers which have been submitted and accepted for publication should be included in the list, the phrase 'in press' replacing volume and page number. Information from manuscripts submitted but not yet accepted should be cited in the text as unpublished observations.

Examples of correct forms of references:

Journals:

1. Brown BR jr, Gandolphi AJ. Adverse effects of volatile anaesthetics *Br J Anaesth* 1987; **59**: 14-23

Chapter in a book:

2. Hull CJ. Opioid infusions for the management of postoperative pain. In: Smith G, Covino BG, eds. *Acute Pain.* London Butterworths, 1985; 155-79

Monographs:

3. Moore, DC. *Regional Block*, 4th Edn. Springfield, Illinois Charles C. Thomas, 1979

Restrict references to those that have direct bearing on the work described and cite only references to books and articles published in *Index Medicus* journals.

It is essential that authors verify the content and detail of references which they list against the original articles, as this responsibility cannot be accepted by either Editors or publishers.

Tables

All tables should be on separate sheets and be capable, with their captions, of interpretation without reference to the text. They should be numbered consecutively with Arabic numerals. Units in which results are expressed should be given in brackets at the top of each column, and not repeated on each line of the table. Ditto signs are not used. Footnotes are not used.

Illustrations

Photographs should be unmounted glossy prints, and should be protected adequately for mailing. Surfaces should not

be marred with clips, pins or by heavy writing on the back. Drawings, charts and graphs should be in black indict ink on white paper and, if in sets, should be presented at a uniform magnification. Illustrations should be clearly numbered on the back, preferably in soft pencil, with reference to the text, and using Arabic numbers. They should be accompanied on a separate sheet by a suitable legend. Lettering should be professional-looking, uniform, preferably in a common typeface, large enough to read at a reduced size, and in proportion to the illustrated material. Lines in the original must also be thick enough to allow for reduction. Magnifications, especially in photomicrographs, should be indicated by a scale on the photograph itself, in order to remain appropriate after reduction. Symbols which are to appear in the figure (and not in the legend) should be chosen from the following available types:

● ○ ■ □ ▼ ▽ ▲ △ ◆ ◇ × +

The names of the author and title of the paper should also be written in soft pencil on the back of the illustrations.

It should be noted that A4-size figures generated by computer are usually unacceptable (see Extended Guide to Contributors—*Br J Anaesth* 2000; **84**: 131-7).

General information

Instructions to the printer. Words to be printed in lowercase italics should be indicated by one underline. Two underlines indicate small capitals, three indicate large capitals and four, italic capitals. A wavy underline indicates a word to be printed in bold type.

Headings in the text. Three possible grades are available, and may be indicated by the following letters of identification.

A **Results (bold)**
B *Lung function studies* (italics, ranged left)
C *Volume.* Large volumes . . . (italics, ranged left, text run on)

Symbols and abbreviations. In accordance with Editorial adoption of SI units, abbreviations and symbols should follow the conventions described in the booklet *Units, Symbols and Abbreviations. A Guide for Biological and Medical Editors and Authors* (D. N. Baron, ed.) (1988), published by and available from The Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE. Words for which abbreviations are not included should be written in full at first mention in the summary and again in the text and followed by the abbreviation in brackets. This will usually be in the form of large capitals without separating points.

Spelling, etc. British spelling should be used with 'z' rather than 's' spelling in, e.g. organize, organization.

Short communications

Authors are encouraged to submit short manuscripts suitable for rapid publication. In general, these should conform to the requirements outlined above, but with the following differences:

Format. Summary; Introduction (not headed); Methods and results; Comment.

Size. Not more than 6 references, 1 table or 1 figure, one-and-a-half pages of printed text (1200 words).

Correspondence

Each issue of the journal will contain correspondence. Correspondence arising from papers in a recent issue is published without delay, and for this reason, will be given priority over that pertaining to original research. The Editor may change, delete or modify in any way all items of correspondence.

All communications designed for publication should be submitted on a separate page in letter quality heavy type (not dot matrix), double-spaced, on one side only of the paper, with a wide margin. Contributors should send three copies of all correspondence to the editor and retain a copy in case of loss. Correspondence must also be submitted on disk. All authors must sign the accompanying submission letter. A fax number and an E-mail address should be supplied.

Proofs

These should be corrected and returned to the publisher by post or fax within 48 h of receipt. Overseas contributors may fax a copy of the proofs to the publisher but should return their proofs by air mail also.

Reprints

Corresponding authors will receive a copy of the journal in which their article appears. Offprints can be supplied if application is made on the order form attached to the proofs. The order form should be returned with the proofs.

IMPORTANT NOTICE TO AUTHORS

Electronic submission of new manuscripts to the British Journal of Anaesthesia. Please note that, from January 2003, the Editorial team requests that all new manuscripts (excluding Letters to the Editor and Book Reviews), be submitted electronically to the *British Journal of Anaesthesia* web site at: http://bja.manuscriptcentral.com

Clear instructions for submission of new manuscripts are available on this web site. If these instructions are not adhered to, difficulty will be experienced in submitting new articles. For an interim period, manuscripts may also be submitted as hard copy to the Editor-in-Chief's office. It is envisaged, however, that this arrangement will be discontinued by the end of 2003.

ANESTHESIA & ANALGESIA

Journal of the International Anesthesia Research Society, the Society of Cardiovascular Anesthesiologists, the Society for Pediatric Anesthesia, the Society for Ambulatory Anesthesia, the International Society for Anaesthetic Pharmacology, and the Society for Technology in Anesthesia

EDITORIAL

789 Droperidol and the FDA

CARDIOVASCULAR ANESTHESIA (Society of Cardiovascular Anesthesiologists)

791 Coronary Artery Bypass Grafting via Sternotomy in Awake Patients
798 Right Ventricular Power and Contractility
805 Remifentanil and Cardiac Surgery
813 Propacetamol After Cardiac Surgery
820 Persistent Pain After Cardiac Surgery
824 Economics of Routine Intraoperative TEE
828 Magnesium and Postoperative Cardiac Arrhythmia
835 Preload Index During Lung Transplant
844 Hemodilution and Hypercoagulability
851 O_2 Delivery in Hemodilution and Beta-Adrenergic Stimulation
858 Effects of Intravenous Fluids on the Hemostatic System
866 Hydroxyethyl Starches and Platelets
870 Novel HemoCue®/Low Hemoglobin and Hemoglobin-Based Oxygen Carriers
874 Left Ventricular Mass in a Patient with Carney's Complex (Case Report)
876 Complication with the Use of an Atrio-Femoral Centrifugal Pump (Case Report)
879 Platelet IIb/IIIa Glycoprotein Inhibitors (Review Article)

PEDIATRIC ANESTHESIA (Society for Pediatric Anesthesia)

889 A Glial-Derived Protein, Neurologic Injury, and Heart Disease

ANESTHETIC PHARMACOLOGY (International Society for Anaesthetic Pharmacology)

893 Neurotransmitter Transporters
900 Alphaxalone Inhibits Nicotinic ACh Receptors
907 Propofol and Spinal $GABA_A$ and Glycine Receptors
915 Propofol and Nucleus Accumbens
920 Propofol and Superoxide Concentration (Brief Report)
923 Pharmacological Properties of Propofol 2% Emulsions
930 Cyclosporine Increases Isoflurane MAC
935 Clonidine and Intrathecal α-Adrenergic Antagonists
940 Monitoring Neuromuscular Blockade and the Diaphragm
944 Midazolam and Diaphragm
948 Acute Morphine Tolerance
952 TNFα and Anesthetic Duration
956 Sublingual Desensitization and Latex Allergy

TECHNOLOGY, COMPUTING, AND SIMULATION

961 Active Warming and Signal Quality of Pulse Oximetry
967 Motion Resistant Pulse Oximetry

PAIN

973 Efficacy of Oral Desipramine in Human Experimental Pain
979 Hyperalgesia and Opioid Abstinence
985 Mexiletine and Gabapentin as Analgesics
992 Local Anesthetics, Amitriptyline: Antioxidants?
997 Glutamate Agonist-Induced Vocalization
1002 Immune Mechanisms of Analgesia (Review Article)
1009 Intrathecal Pump and Acute Mental Status Changes (Case Report)

ECONOMICS, EDUCATION, AND HEALTH SYSTEMS RESEARCH

1012 The Cochrane Anesthesia Review Group (Special Article)
1019 Criteria for Selection of Academic Chairs (Special Article)
1024 Controlled Substance Abuse in Anesthesiology

CRITICAL CARE AND TRAUMA

1031 CPR and Hypertonic-Hyperoncotic Solutions'
1037 Endotracheal Epinephrine: A Call for Larger Doses

NEUROSURGICAL ANESTHESIA

1042 Brain Oxygen Partial Pressure and Cerebral Energetic Threshold Levels
1049 Hypercapnia Increases Systolic Cerebrospinal Fluid Peak Velocity
1052 Dexmedetomidine Decreases Cerebral Blood Flow
1060 Percutaneous Vertebroplasty and Pulmonary Embolism (Case Report)

OBSTETRIC ANESTHESIA

1063 In Vitro Fertilization-Induced Coagulation Changes

REGIONAL ANESTHESIA

1067 Median Transsacral Epidural Block
1071 Anatomy of the Sciatic Nerve, Anterior Sciatic Nerve Block
1075 Axillary Versus Humeral Regional Block
1080 Nerve/Muscle Blood Flow with Lidocaine ± Adrenergics
1087 Broken Epidural Catheter (Case Report)

GENERAL ARTICLES

1090 Laryngoscopy and Tracheal Intubation with a Dental Mirror
1094 Laryngeal Tube Versus Laryngeal Mask Airway
1098 Sleep Apnea and Anesthesia
1103 Capsicum Plaster, Acupuncture, and PONV
1108 Legacy of Albert Faulconer, Jr. (Special Article)
1112 Laryngeal Trauma During Awake Fiberoptic Intubation (Case Report)
1115 MEETING REPORT
1119 LETTERS TO THE EDITOR
1129 BOOK AND MULTIMEDIA REVIEWS

ISSN 0003-2999 Volume 95, Number 4, October 2002
www.anesthesia-analgesia.org

Visit the
ISAP Website
www.isaponline.org

OXFORD JOURNALS

Medicine

www.oupjournals.org/medicine/?f2

Oxford University Press publishes some of the most respected and highly-cited medical journals in the world including:

BJA: British Journal of Anaesthesia

Human Reproduction

Journal of Antimicrobial Chemotherapy

Nephrology Dialysis Transplantation

Rheumatology

FULL TEXT *now online*

If you are a current print subscriber (institutional or personal), visit **www3.oup.co.uk/Register/?f2** to activate your online access.

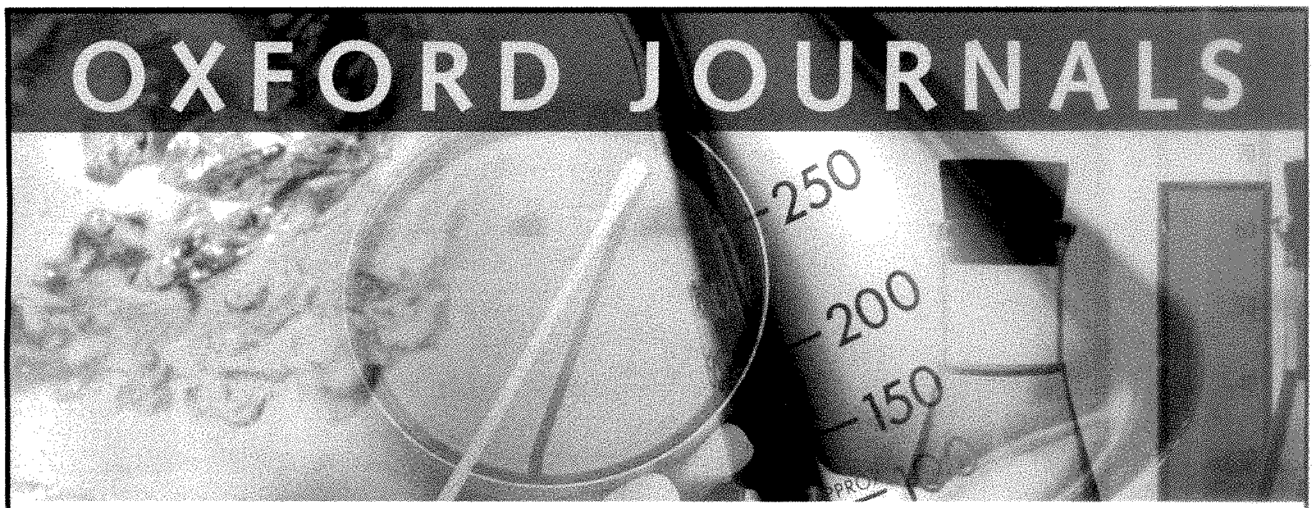
FREE @ the web site:

- **tables of contents by e-mail**
- **sample issues**
- **abstracts and tables of contents**
- **instructions to authors**

To subscribe to the above journals, visit the web site @
www.oupjournals.org/medicine/?f2

For further information please contact:
Journals Dept. • E-mail: jnls.cust.serv@oup.co.uk
Tel: +44 1865 267907 • Fax: +44 1865 267835
In the Americas, please contact:
Journals Dept. • E-mail: jnlorders@oup-usa.org
Tel: +1 800 852 7323 (USA/Canada) or +1 919 677 0977
(outside USA/Canada) • Fax: +1 919 677 1714

OXFORD
UNIVERSITY PRESS



BJA CEPD Reviews

www.oupjournals.org/list/bjarev/?f2

Editor-in-Chief: David J Rowbotham

BJA CEPD Reviews is a joint venture of the British Journal of Anaesthesia and The Royal College of Anaesthetists in collaboration with the Intensive Care Society and Pain Society.

The purpose of ***BJA CEPD Reviews*** is the publication of material to support the continuous medical education and professional development of specialists in anaesthesia, critical care medicine and pain

To subscribe, visit the web site @
www.oupjournals.org/list/bjarev/?f2

For further information please contact:
Journals Dept. • E-mail: jnls.cust.serv@oup.co.uk
Tel: +44 1865 267907 • Fax: +44 1865 267835
In the Americas, please contact:
Journals Dept. • E-mail: jnlorders@oup-usa.org
Tel: +1 800 852 7323 (USA/Canada) or +1 919 677 0977
(outside USA/Canada) • Fax: +1 919 677 1714

OXFORD
UNIVERSITY PRESS

OXFORD JOURNALS

QJM - An International Journal of Medicine

Editor: Dr. Christopher N. Martyn

www.qjmed.oupjournals.org/?f2

QJM is a long-established, leading general medical journal. It focuses on internal medicine and publishes peer-reviewed articles which promote medical science and practice.

7 reasons to publish in QJM

1 Impact factor of 2.25
2 Rapid publication - about 10 weeks post acceptance
3 Opportunity for in-depth articles and reviews
4 Influential readership that includes a wide range of specialists
5 Online manuscript submissions from 2002 - e-mail submissions already accepted
6 Wide usage of QJM online and extensive links ensure a high profile for all papers
7 Inclusion in all major indexing/abstracting services

➲ FULL TEXT *now online*

If you are a current print subscriber (institutional or personal), visit **www3.oup.co.uk/Register/?f2** to activate your online access.

➲ FREE @ the web site:

- tables of contents by e-mail
- sample issue
- abstracts and tables of contents
- instructions to authors

To subscribe, visit the web site @
www.qjmed.oupjournals.org/?f2

For further information please contact:
Journals Dept. • E-mail: jnls.cust.serv@oup.co.uk
Tel: +44 1865 267907 • Fax: +44 1865 267835

In the Americas, please contact:
Journals Dept. • E-mail: jnlorders@oup-usa.org
Tel: +1 800 852 7323 (USA/Canada) or +1 919 677 0977
(outside USA/Canada) • Fax: +1 919 677 1714

OXFORD
UNIVERSITY PRESS

TWO DAY COURSE ON
TRANSOESOPHAGEAL ECHOCARDIOGRAPHY
Thursday 6th - Friday 7th March 2003
St George's Hospital, London, United Kingdom

St George's Hospital Medical School
University of London

Course Directors:
Dr Stephen Brecker and Mr Graham Leech
with **International Faculty**

Topics will include:
Live ASD Closure.-.Live Anatomy - Endocarditis
Prosthetic Valves - Intra-operative Applications
Congenital Disease - Aortic Dissection
Assessing Mitral Valve Anatomy
TOE in Anaesthesia - Ventricular function

For further details please contact:
Dr S Brecker, Cardiology
St George's Hospital, Blackshaw Road,
London SW17 0QT
Tel: +44 (0)20-8725-1390 Fax: +44 (0)20-8725-0211
e-mail: cmurphy@sghms.ac.uk

ANAESTHETISTS
Australia, New Zealand & UK

The 'Wavelength' commitment to quality, integrity and confidentiality make us the recruitment company of choice when it comes to working overseas/ internationally. We currently have the following positions:

- **Australia** - ICU and Anaesthetic posts - multiple locations
- **New Zealand** - Anaesthetist - 2 coastal hospitals (North and South Islands)
- **UK** - Anaesthetic and ICU - North of England

All other enquiries welcome. For more information please call **UK (0709) 236 2513** or in **Australia (+61 2) 9332 3368**, e-mail us on **info@wave.com.au** or apply on-line.

wavelength
CONSULTING
www.**wave**.com.au

INTERNATIONAL MEDICAL RECRUITMENT AND LOCUM SERVICES

PROFESSOR AND CHAIR
DEPARTMENT OF ANESTHESIOLOGY
THE UNIVERSITY OF MISSISSIPPI MEDICAL CENTER • JACKSON

The University of Mississippi Medical Center is seeking nominations and applications for the position of professor and chair of the Department of Anesthesiology.

The University Medical Center, the state's only health sciences campus, houses the Schools of Medicine, Nursing, Health Related Professions, Dentistry, and Graduate Studies in the Health Sciences. The campus is the site of a 722-bed university hospital, and there are several clinics on and adjacent to the campus. Inpatients approximate 27,000 annually, and there are more than 418,000 outpatient and emergency visits every year.

The Department of Anesthesiology has 18 full-time and two part-time faculty members. The department's divisions include cardiothoracic anesthesia, neuro-anesthesia, pediatric anesthesia, regional anesthesia, obstetrical anesthesia, and pain management. The Medical Center's faculty totals 776.

The largest expansion project in the Medical Center's history, totaling $211 million, was completed in 1999. The project included a new children's hospital, a women and infants' hospital, an imaging center, two parking garages, a student union with a conference center, an addition to the School of Nursing and a new building for the School of Health Related Professions. A 92-bed adult critical care hospital opened last year. A $124 million building project is underway. This includes a new 256-bed adult hospital with a capacity for expansion to 384 beds that will be completed in 2004, a new cancer institute, addition of an operating suite and ambulatory surgery unit to the Children's Hospital, a classroom building, and expansion of the Arthur C. Guyton Research Complex.

The University Medical Center is located in Jackson, the state's capital. Jackson is at the crossroads of the south, located halfway between Atlanta and Dallas and New Orleans and Memphis. The tri-county, metropolitan area census is approximately 400,000. The city hosts a variety of arts attractions including the Mississippi Symphony, the Mississippi Opera, New Stage Theatre and the quadrennial International Ballet Competition. Recreational facilities include a 33,000-acre reservoir, just 15 minutes from the University Medical Center, numerous public tennis courts and golf courses, navigable waterways, and more than 2,650 acres of city parks and play grounds.

Candidates for this position should have administrative experience and an exceptional background in teaching, research, and clinical service. Candidates should be nationally recognized in academic anesthesiology. Individuals must be eligible for medical licensure in Mississippi.

Applications will be taken until the position is filled. Contact Dr. William W. Turner, Jr., Chair, Anesthesiology Advisory Committee, c/o Department of Surgery, University of Mississippi Medical Center, 2500 North State Street, Jackson, Mississippi 39216-4505.

The University of Mississippi Medical Center is an equal opportunity employer. M/F/D/V.

Anaesthetist/s

Specialist Register

Our client, a private hospital in the London area, is seeking to add to its complement of medical staff with the appointment of one full-time or two part-time Anaesthetists.

Excellent working conditions and support staff.

Please submit a brief CV to

MRP Recruitment Advertising
12 Conway Gardens
Enfield Middlesex EN2 9AD

14th South West Thames Anaesthesia Update

27-31 January 2003
Belle Plagne, French Alps

Open to all Anaesthetists

The Scientific Programme will include lectures, and discussions on:

- Acute and Chronic Pain
- Paediatric Update
- Day Case Anaesthesia
- Obstetric Anaesthesia
- Neurology and Anaesthesia
- ITU and Relevant Medical Topics
- Cardiothoracic topics
- Radiology for Anaesthetist
- New Drugs Update
- Training &Education
- Anaesthetic Audit
- Free papers
- Panel Discussions
- Workshops

Guest Speakers

Videos on New Equipment, Drugs and Techniques

Anaesthetists in training presenting papers are eligible for prizes.

Deadline for abstracts: December 9th 2002

This Meeting is approved for CME purposes

For further details, please contact:

Dr J.B. Liban
Department of Anaesthesia
St George's Hospital
Blackshaw Road,
London SW17 0QT

Fax: +44 (0)20 8725 3135
Tel: +44 (0)20 8725 0018
email: liban@mailbox.co.uk

www.doctorsupdates.com

medical education in a perfect location

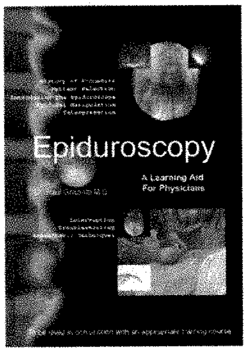
EPIDUROSCOPY

A learning aid for physicians

60 minutes of high quality digital video on DVD format

Includes sections on

- History of procedure
- Patient selection
- Introducing the scope
- Manipulating the scope in the epidural space
- Interpreting findings
- Interventional techniques
- Troubleshooting
- Anaesthetic considerations



Produced by Dr Paul Graziotti MBBS FFARACS FFARCS FFPMANZCA, Pain Management Physician

The perfect refresher tool for beginning and established practitioners.

Available for purchase, price £80, at www.ipmt.net
Email: info@ipmt.net Phone: +61 89 386 5891
Fax: +61 89 386 5927

The University of Iowa Department of Anesthesia
Faculty Position: Human Patient Simulator Director

The University of Iowa, Department of Anesthesia is actively recruiting an outstanding clinician and educator for a leadership role in our department through leadership of our human patient simulator program. We are interested in candidates with a desire to direct and develop our human patient simulator education suite as a means of educating our medical students, physician residents, and other professionals in a unique and challenging ways. We are looking for candidates to be appointed to either our tenure or non-tenure clinical track in any of our academic ranks.

The Department is interested in anesthesiologists interested in working in a collegial setting where research, clinical care and education are all valued. The University of Iowa is located in Iowa City, a vibrant community located in the rolling hills of southeastern Iowa. The community offers excellent schools, quality entertainment, literary, musical and cultural opportunities and Big-10 sporting events. Please send CV and contact:

David L. Brown, M.D., Professor and Head
Department of Anesthesia, The University of Iowa
200 Hawkins Drive, Room 6618 JCP
Iowa City, Iowa 52242-1079
Telephone (319) 356-2382 or Fax (319) 356-4130

The University of Iowa is an Affirmative Action and Equal Opportunity Employer. Women and minorities are strongly encouraged to apply.

BJA
International Journal of Anaesthesia
Volume 89 Number 6 December 2002

EDITORIALS

807 I. Confidence in statistical analysis
T. Asai

810 II. Why does smoking protect against PONV?
B. P. Sweeney

CLINICAL INVESTIGATIONS

814 Phase behaviour of premixed 0.25% isoflurane in 50% nitrous oxide and 50% oxygen
M. E. Tunstall and J. A. Ross

820 Simulated use of premixed 0.25% isoflurane in 50% nitrous oxide and 50% oxygen
J. A. Ross and M. E. Tunstall

825 Equipment problems during anaesthesia—are they a quality problem?
S. Fasting and S. E. Gisvold

832 Stereoselective *in vitro* degradation pattern of mivacurium in human plasma
J. Laurin, F. Donati and F. Varin

839 Pharmacogenetics of codeine metabolism in an urban population of children and its implications for analgesic reliability
D. G. Williams, A. Patel and R. F. Howard

846 Plasma lidocaine concentrations following insertion of 2% lidocaine gel into the uterine cavity after uterine balloon thermal ablation
G. F. Rousseau, M. Oram, J. Barrington, M. Priston and M. Swart

849 Effects of intramuscular administration of lidocaine or bupivacaine on induction and maintenance doses of propofol evaluated by bispectral index
M. Senturk, K. Pembeci, F. Menda, T. Ozkan, B. Gucyetmez, M. Tugrul, E. Camci and K. Akpir

853 Sevoflurane anaesthesia in children after induction of anaesthesia with midazolam and thiopental does not cause epileptiform EEG
K. Nieminen, S. Westerèn-Punnonen, H. Kokki, H. Yppärilä, A. Hyvärinen and J. Partanen

857 Esmolol prevents movement and attenuates the BIS response to orotracheal intubation
C. Menigaux, B. Guignard, F. Adam, D. I. Sessler, V. Joly and M. Chauvin

863 Patient satisfaction with anaesthesia care: development of a psychometric questionnaire and benchmarking among six hospitals in Switzerland and Austria
T. Heidegger, Y. Husemann, M. Nuebling, D. Morf, T. Sieber, A. Huth, R. Germann, P. Innerhofer, A. Faserl, C. Schubert, C. Geibinger, K. Flückiger, T. Coi and G. Kreienbühl

873 Stress in UK intensive care unit doctors
S. Coomber, C. Todd, G. Park, P. Baxter, J. Firth-Cozens and S. Shore

LABORATORY INVESTIGATIONS

882 Comparison of effects of anandamide at recombinant and endogenous rat vanilloid receptors
J. C. Jerman, J. Gray, S. J. Brough, L. Ooi, D. Owen, J. B. Davis and D. Smart

888 Electrophysiological effects of morphine in an *in vitro* model of the 'border zone' between normal and ischaemic–reperfused guinea-pig myocardium
A. Yvon, J.-L. Hanouz, X. Terrien, P. Ducouret, R. Rouet, H. Bricard and J.-L. Gérard

896 Sevoflurane preconditions stunned myocardium in septic but not healthy isolated rat hearts
R. Serita, H. Morisaki, K. Ai, Y. Morita, Y. Innami, T. Satoh, S. Kosugi, Y. Kotake and J. Takeda

REVIEW ARTICLE

904 Parkinson's disease and anaesthesia
G. Nicholson, A. C. Pereira and G. M. Hall

SHORT COMMUNICATIONS

917 What information do anaesthetists provide for patients?
G. M. M. Thoms, G. A. McHugh and J. A. Lack

919 Lactic acidosis in the rectal lumen of patients with septic shock measured by luminal equilibrium dialysis
V. Due, J. Bonde, K. Espersen, T. H. Jensen and A. Perner

922 Bacterial contamination of epidural needles after multiple skin passes
C. Orlikowski, P. M. Majedi and A. D. Keil

CASE REPORTS

925 Intrathecal morphine overdose during combined spinal–epidural block for Caesarean delivery
M. Cannesson, N. Nargues, B. Bryssine, R. Debon, E. Boselli and D. Chassard

927 Management of a known difficult airway in a morbidly obese patient with gross supraglottic oedema secondary to thyroid disease
M. Hariprasad and G. J. Smurthwaite

930 Probable allergic reaction to cyclosporin and early formation of thrombi on a pulmonary artery catheter: two unusual complications during bilateral lung transplantation
N. Dalibon, M. Stern, P. Bonnette, G. Dreyfus and M. Fischler

934 CORRESPONDENCE

940 BOOK REVIEWS

945 INDEX TO VOLUME 89

PROFESSOR AND CHAIR DEPARTMENT OF ANESTHESIOLOGY

THE UNIVERSITY OF MISSISSIPPI MEDICAL CENTER • JACKSON

The University of Mississippi Medical Center is seeking nominations and applications for the position of professor and chair of the Department of Anesthesiology.

The University Medical Center, the state's only health sciences campus, houses the Schools of Medicine, Nursing, Health Related Professions, Dentistry, and Graduate Studies in the Health Sciences. The campus is the site of a 722-bed university hospital, and there are several clinics on and adjacent to the campus. Inpatients approximate 27,000 annually, and there are more than 418,000 outpatient and emergency visits every year.

The Department of Anesthesiology has 18 full-time and two part-time faculty members. The department's divisions include cardiothoracic anesthesia, neuro-anesthesia, pediatric anesthesia, regional anesthesia, obstetrical anesthesia, and pain management. The Medical Center's faculty totals 776.

The largest expansion project in the Medical Center's history, totaling $211 million, was completed in 1999. The project included a new children's hospital, a women and infants' hospital, an imaging center, two parking garages, a student union with a conference center, an addition to the School of Nursing and a new building for the School of Health Related Professions. A 92-bed adult critical care hospital opened last year. A $124 million building project is underway. This includes a new 256-bed adult hospital with a capacity for expansion to 384 beds that will be completed in 2004, a new cancer institute, addition of an operating suite and ambulatory surgery unit to the Children's Hospital, a classroom building, and expansion of the Arthur C. Guyton Research Complex.

The University Medical Center is located in Jackson, the state's capital. Jackson is at the crossroads of the south, located halfway between Atlanta and Dallas and New Orleans and Memphis. The tri-county, metropolitan area census is approximately 400,000. The city hosts a variety of arts attractions including the Mississippi Symphony, the Mississippi Opera, New Stage Theatre and the quadrennial International Ballet Competition. Recreational facilities include a 33,000-acre reservoir, just 15 minutes from the University Medical Center, numerous public tennis courts and golf courses, navigable waterways, and more than 2,650 acres of city parks and play grounds.

Candidates for this position should have administrative experience and an exceptional background in teaching, research, and clinical service. Candidates should be nationally recognized in academic anesthesiology. Individuals must be eligible for medical licensure in Mississippi.

Applications will be taken until the position is filled. Contact Dr. William W. Turner, Jr., Chair, Anesthesiology Advisory Committee, c/o Department of Surgery, University of Mississippi Medical Center, 2500 North State Street, Jackson, Mississippi 39216-4505.

The University of Mississippi Medical Center is an equal opportunity employer. M/F/D/V.

JOURNAL ADVERTISING

To advertise in this publication contact

PRC ASSOCIATES

Advertisement Managers

PRC ASSOCIATES LTD
THE ANNEXE, FITZNELLS MANOR, CHESSINGTON ROAD, EWELL VILLAGE, SURREY KT17 1TF, UK
TELEPHONE: +44 (0)20 8786 7376 FAX: +44 (0)20 8786 7262
EMAIL: mail@prcassoc.co.uk

Editorial Board

Editor-in-Chief

JENNIFER M. HUNTER, Professor of Anaesthesia, *University of Liverpool*

Editors

G. B. DRUMMOND, Senior Lecturer in Anaesthesia, *Royal Infirmary, Edinburgh*
P. M. HOPKINS, Professor of Anaesthesia, *University of Leeds*
D. G. LAMBERT, Reader in Anaesthetic Pharmacology, *University of Leicester*
D. J. ROWBOTHAM, Professor of Anaesthesia and Pain Management, *University of Leicester*

Board Members

F. BONNET, Professor of Anaesthesia, *Assistance Publique Hopitaux de Paris*
H. F. GALLEY, Senior Lecturer in Anaesthesia and Intensive Care, *University of Aberdeen*
G. M. HALL, Professor of Anaesthesia, *University of London*
S. J. HOWELL, Senior Lecturer in Anaesthesia, *University of Leeds*
P. HUTTON, President, *Royal College of Anaesthetists*
D. M. JUSTINS, Vice-president, *Royal College of Anaesthetists*
P. A. LONNQVIST, Associate Professor of Paediatric Anaesthesia and Intensive Care, *Lingrens Children's Hospital, Stockholm, Sweden*
R. P. MAHAJAN, Reader in Anaesthesia, *University of Nottingham*
R. D. MILLER, Professor of Anesthesia, *University of California, San Francisco*
I. POWER, Professor of Anaesthesia, Critical Care and Pain Medicine, *University of Edinburgh*
H.-J. PRIEBE, Professor of Anaesthesia, *University of Freiburg, Germany*
C. S. REILLY (Treasurer), Professor of Anaesthesia, *University of Sheffield*
J. W. SEAR, Professor of Anaesthesia, *University of Oxford*
P. J. SIMPSON, Vice-president, *Royal College of Anaesthetists*
G. SMITH (Chairman), Professor of Anaesthesia, *University of Leicester*
J. R. SNEYD, Professor of Anaesthesia, *Peninsula Medical School, Plymouth*
D. R. SPAHN, Professor of Anaesthesia, *University Hospital, Lausanne, Switzerland*
N. R. WEBSTER (Secretary), Professor of Anaesthesia, *University of Aberdeen*
J. A. W. WILDSMITH, Professor of Anaesthesia, *Ninewells Hospital and Medical School, Dundee*
J. D. YOUNG, Reader in Anaesthesia, *Radcliffe Infirmary, Oxford*

International Board Members

F. CARLI, Wesley Bourne Professor and Chairman, Department of Anesthesia, *McGill University, Montreal, Canada*
K. HIROTA, Department of Anesthesiology, *University of Hirosaki, Japan*

Assistant Editors

R. S. JONES, Emeritus Professor of Veterinary Anaesthesia, *University of Liverpool*
B. V. S. MURTHY, Consultant Anaesthetist, *Royal Liverpool University Hospital*

Production Staff

E. GOODING, Senior Production Editor, *Oxford University Press*
H. J. LAMB, Production Editor, *Oxford University Press*
G. G. R. T. MUCKLOW, Editorial Assistant, *Oxford University Press*
Please visit the Journals's World Wide Web site at http://bja.oupjournals.org

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

General Information

Subscriptions

All Fellows of the College, world-wide, should notify changes of address directly to the Royal College of Anaesthetists.

An annual subscription to *BJA* comprises 12 issues (two volumes of 6 issues), with Author and Subject Indexes. Subscriptions are entered on a calendar year basis only. Please add local sales tax to the prices quoted. Prices include postage by surface mail, or for subscribers in the USA and Canada by Airfreight, or in Japan, Australia, New Zealand, and India by Air Speeded Post. Airmail rates are available on request.

Annual subscription rate 2002

Full text print version of the *BJA*

Full rate (institutions and individuals): UK and Europe £255, Rest of World US$400

Trainees: UK and Europe £120, Rest of World US$190

ESA/EACTA/EAA/ESRA/JSA/IARS members: UK and Europe £120, Rest of the World US$190

Single issue: UK and Europe £27, Rest of World US$38

Orders

Orders and payments from, or on behalf of, subscribers in the various geographical areas shown below should be sent to the office indicated. Payment may be made by the following methods: cheque (made payable to Oxford University Press); National Girobank (Account 500 1056); credit card (Mastercard, Visa, American Express); UNESCO coupons; direct debit (please ask for details). Bankers: Barclays Bank plc, PO Box 333, Oxford, UK; Code 20-65-18; Account 00715654.

The Americas: Oxford University Press Inc., 2001 Evans Road, Cary, NC 27513, USA.

Japan: available from the following agents:

Kinokuniya Company Ltd, Journal Department, PO Box 55, Chitose, Tokyo, 156 Japan.
Maruzen Company Ltd, Journal Division, PO Box 5050, Tokyo International, 100-31 Japan.
Usaco Corporation, 13-12 Shimbashi 1-chome, Minato-ku, Tokyo, 105 Japan.

Rest of the world: Oxford University Press, Journals Subscriptions Department, Great Clarendon Street, Oxford OX2 6DP, UK. Tel +44 (0)1865 267907; Fax: +44 (0)1865 267485; E-mail: jnl.orders@oup.co.uk

Please address orders and enquiries about availability as follows: *For current volume and back numbers from Vol. 82 onwards* to Oxford University Press. *For Vols 1-81* to Periodicals Service Company, 11 Main Street, Germantown, NY 12526, USA.
Tel: +1 (518) 537 4700; Fax: +1 (518) 537 5899.

Advertising

Advertising enquiries should be addressed to Peter Carpenter, PRC Associates, The Annexe, Fitznells Manor, Chessington Road, Ewell Village, Surrey KT17 1TF, UK.
Tel: +44 (0)20 8786 7376; Fax: +44 (0)20 8786 7262;
E-mail: mail@prcassoc.co.uk

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

All rights reserved; no part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise without the prior written permission of the *British Journal of Anaesthesia*, requests for which should be addressed to the Publisher, or a licence permitting restricted copying issued in the UK by the Copyright Licensing Agency Ltd, 90 Tottenham Court Road, London W1P 9HE, or in the USA by the Copyright Clearance Center, 222 Rosewood Drive, Danvers, MA 01923. For those in the US/Canada not registered with CCC, articles can be obtained by fax in 48 hours by calling: WISE for MedicineTM 1-800-667-WISE.

British Journal of Anaesthesia (ISSN 0007-0912) is published monthly by Oxford University Press, Oxford, UK. Annual subscription price is US$400. *British Journal of Anaesthesia* is distributed by Mercury International, 365 Blair Road, Avenel, NJ 07001, USA. Periodicals postage paid at Rahway, New Jersey, and additional entry points.

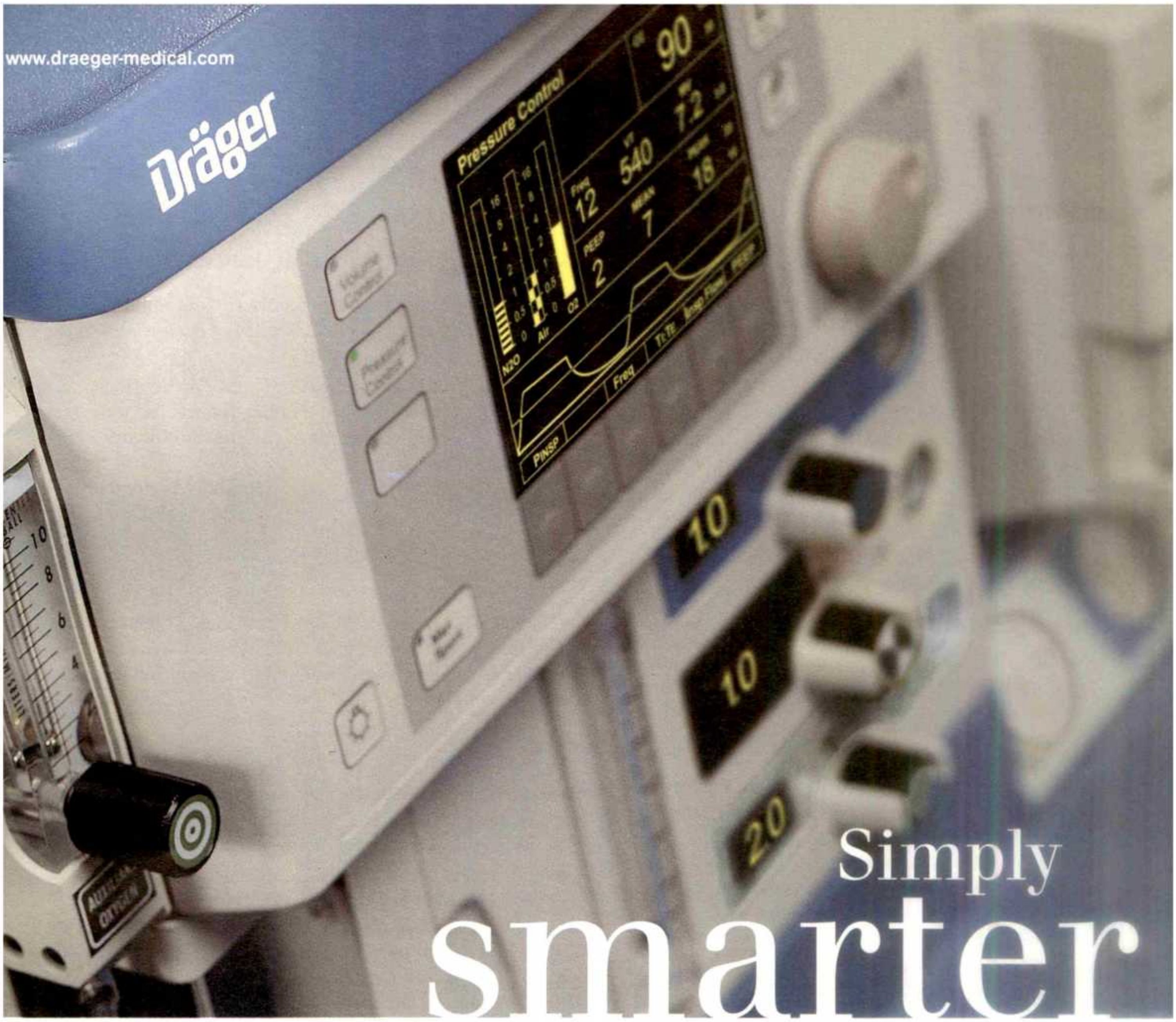
US Postmaster: send address changes to *British Journal of Anaesthesia*, c/o Mercury International, 365 Blair Road, Avenel, NJ 07001, USA.

Disclaimer

Whilst every effort is made by the publishers and editorial committee to see that no inaccurate or misleading data, opinions or statements appear in this Journal, they wish to make it clear that the data and opinions appearing in the articles and advertisements herein are the responsibility of the contributor or advertiser concerned. Accordingly, the publisher and the editorial committee and their respective employees, officers and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinions or statements. While every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described within this Journal, should only be followed in conjunction with the drug manufacturer's own published literature.

Printed by Information Press Ltd, Oxford, UK.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002



The Fabius GS combines superior performance with ease of use. An electronically controlled piston ventilator provides both volume control and true pressure control ventilation modes without weight or age restrictions. The revolutionary user interface is simple, intuitive and allows the electronic capture of fresh gas data for inclusion in a perioperative information system. Integrated equipment mounting rails and a unique CPU storage area allow the user to create their own tailor-made ergonomic workstation.

Fabius GS is one of *three* pillars of innovation that mark a revolutionary new chapter in Dräger Medical's anesthesia device technology.

The essence of anesthesia.

Dräger
MEDICAL

Editorial Notices

Important Notice to Authors

Electronic Submission of New Manuscripts to *The British Journal of Anaesthesia*

Please note that, from January 2003, the Editorial team requests that all new manuscripts (excluding Letters to the Editor and Book Reviews) be submitted electronically to the *British Journal of Anaesthesia* web site at: http://bja.manuscriptcentral.com

Clear instructions for submission of new manuscripts are available on this web site. If these instructions are not adhered to, difficulty will be experienced in submitting new articles. For an interim period, manuscripts may also be submitted as hard copy to the Editor-in-Chief's office. It is envisaged, however, that this arrangement will be discontinued by the end of 2003.

Jennifer M. Hunter
Editor-in-Chief

Royal Medical Benevolent Fund

President's Christmas Message for 2002

Readers of the *British Journal of Anaesthesia*, in recent years, have been generous in their response to the Christmas Appeal on behalf of the Royal Medical Benevolent Fund.

As newly elected President of the Fund, I have seen the support it gives to those doctors and their dependants who are less fortunate than ourselves. Whether as a result of health problems, an unexpected family tragedy, or other reasons, there are all too many doctors and their families who are in great need—and never is that need more evident than at Christmas.

Since 1870, the President of the Fund has made a Christmas appeal to those doctors in happier circumstances to help provide a gift, or more usually, a little money. This helps to transform a cheerless Christmas into a very happy one, especially when children are involved, as they frequently are. Last year's appeal raised some £74,000. Let us try to exceed this and establish a new record. Please consider sending a donation, preferably using gift aid, and help brighten Christmas 2002 for many needy colleagues and their dependants. Contributions marked 'Christmas Appeal' may be sent to the RMBF, 24 King's Road, Wimbledon, London SW19 8QN or to the Treasury of your local guild of this Fund. Thank you.

To those of you who may already have contributed—a very warm thank you.

Royal Medical Benevolent Fund

Are you a current or very recently retired doctor? Would you like to help colleagues less fortunate than yourself? Our recent cases include doctors who have suffered strokes, cancer, multiple sclerosis, paralysis after serious road accidents, blindness, schizophrenia, manic depression, dependency and the suicide of a partner. A growing number are junior doctors with limited pension entitlement and insurance cover.

Do you have a few hours to help?

Medical Liaison Officer

The aim is to ensure doctors and their families in your area are aware of the financial help which may be available from the RMBF in time of crisis, and in particular to:

- Liaise with local hospitals, medical centres, medical societies and associations, to seek to ensure that doctors and their families are aware of the type of help the Fund may be able to provide.
- To provide information about the RMBF to any colleagues and their dependants likely to need assistance and to advise the Fund where appropriate.
- To advise the Fund of any planned medical conferences, exhibitions or meetings in your area where it might be possible for the RMBF to be represented.

We need career grade doctors who are currently practising or very recently retired (i.e. within the last two years), with good contacts within the medical world and able to commit on average a couple of hours a week to help the Fund.

For further information about becoming a volunteer Medical Liaison Officer for the Fund, please contact: Royal Medical Benevolent Fund, 24 King's Road, Wimbledon, London SW19 8QN. Tel: +44 (0)208 540 9194; E-mail: info@rmbf.org

Help!

Have you had a patient showing signs of hypoxic brain damage when the Holmann laser was used, or urea renal

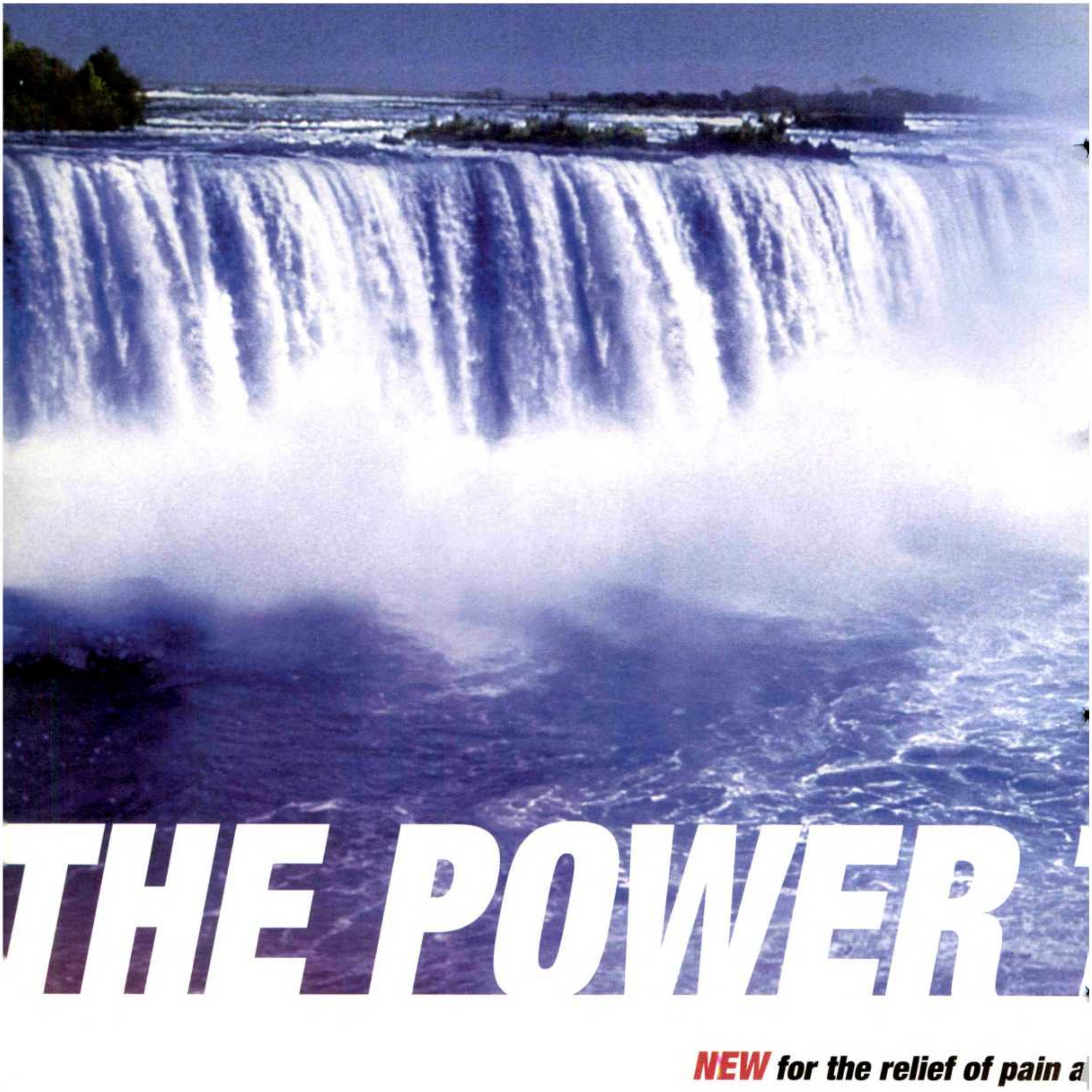
© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Primus, Dräger Medical's next-generation anesthesia workstation, is designed to be your personal anesthesia assistant in the most demanding operations and everyday clinical routine. And like every good assistant, Primu supports your decision-making for improved efficiency in low-flow delivery and ventilation. Primus sets new standards in perioperative therapy with its new, innovative intensive care ventilator performance. A modular design, open-platform architecture and optional upgrade packages ensure you get a customized personal assistant to meet your specific requirements, e.g. with the patient monitoring system of your choice. So you can enjoy optimized processes in the perioperative environment.

Primus is one of *three* pillars of innovation that mark a revolutionary new chapter in Dräger Medical's anesthesia device technology.

The essence of anesthesia.

Dräger
MEDICAL



NEW for the relief of pain a

'RCOXIA® (etoricoxib)
BRIDGED PRODUCT INFORMATION
fer to Summary of Product Characteristics before prescribing.

RESENTATION
blets: 60 mg, 90 mg and 120 mg tablets each containing 60 mg, 90 mg or 120 mg of etoricoxib
pectively.

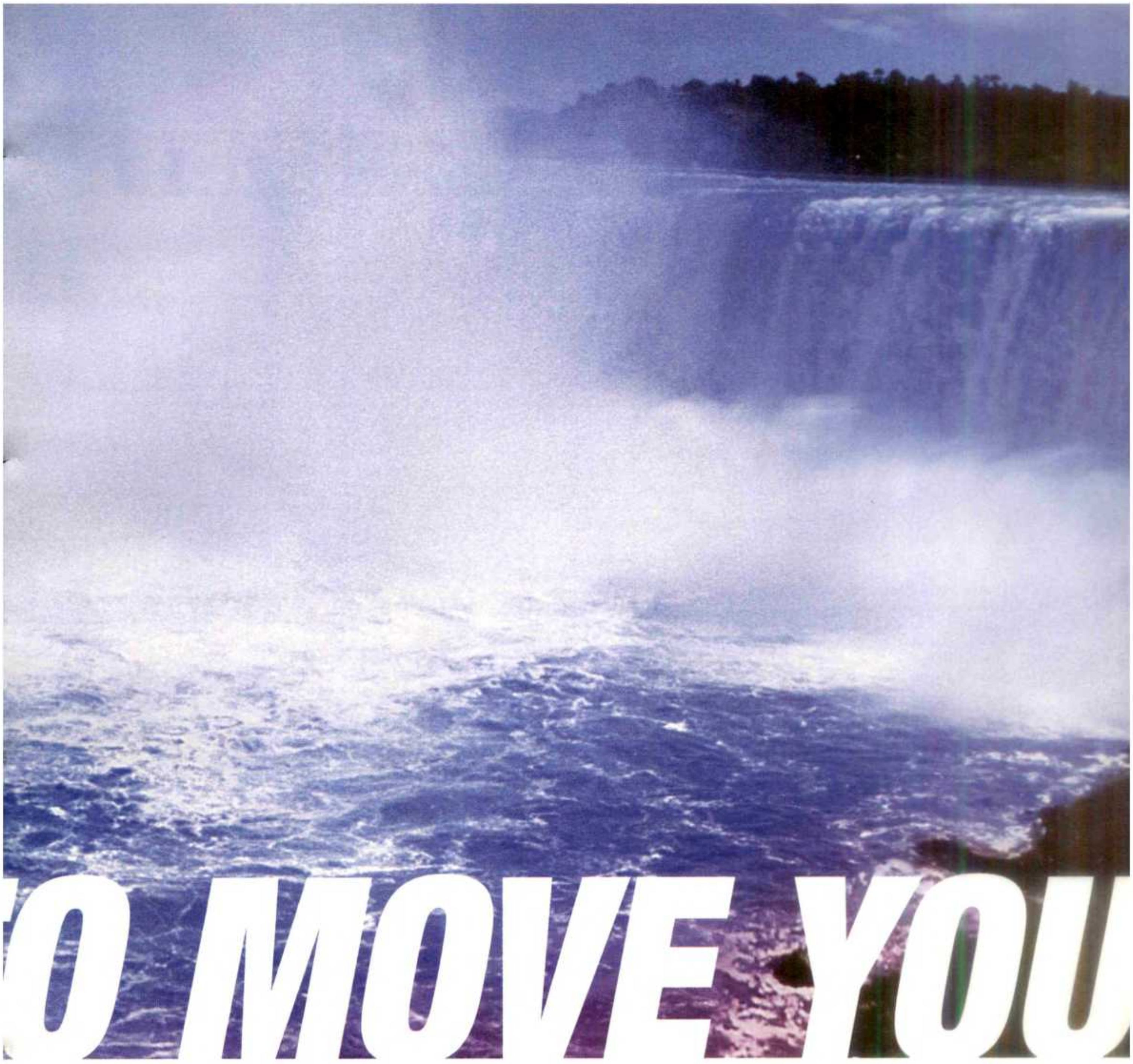
ES
nptomatic relief of osteoarthritis, rheumatoid arthritis (RA) and the pain and signs of
lammation associated with acute gouty arthritis.

OSAGE AND ADMINISTRATION
ce orally with or without food. Onset of action may be faster when administered without
d, and should be considered when rapid relief is needed. *Osteoarthritis:* 60 mg once daily.
eumatoid arthritis: 90 mg once daily. *Acute gouty arthritis:* 120 mg once daily for the acute
nptomatic period only. Each dose above is the maximum recommended dose for each
ndition. *Renal insufficiency:* No dosage adjustment necessary for patients with creatinine
arance ≥30 ml/min. *Hepatic insufficiency: mild* (Child-Pugh score 5-6): do not exceed a
e of 60 mg; *moderate* (Child-Pugh score 7-9): **do not exceed 60 mg every other day**.

ONTRA-INDICATIONS
persensitivity to any component of this product. Active peptic ulceration or gastro-intestinal
) bleeding. Severe hepatic dysfunction (Child-Pugh score >9). Estimated creatinine clearance
0 ml/min. Patients who have developed signs of asthma, acute rhinitis, nasal polyps,
gioneurotic oedema or urticaria after aspirin or other NSAIDs. Pregnancy and lactation.
Children and adolescents under 16 years of age. Inflammatory bowel disease. Severe congestive heart failure.

PRECAUTIONS

Cardiovascular: COX-2-selective inhibitors are not a substitute for aspirin for cardiovascular prophylaxis due to their lack of effect on platelets. Because etoricoxib does not inhibit platelet aggregation, do not discontinue antiplatelet therapies and if indicated, consider them in patients at risk for or with a history of cardiovascular or other thrombotic events. Exercise caution in patients with a medical history of ischaemic heart disease. Take appropriate measures and consider discontinuing etoricoxib therapy if there is clinical evidence of symptomatic deterioration in the condition of these patients. Lack of antiplatelet activity should also be considered in patients with a history of cerebrovascular disease. *Renal effects:* Consider monitoring renal function in patients with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis. *Fluid retention, oedema and hypertension:* Exercise caution in patients with a history of cardiac failure, left ventricular dysfunction, or hypertension and pre-existing oedema from any other reason, as fluid retention and oedema have been observed in patients taking etoricoxib. Take appropriate measures, including discontinuation of etoricoxib where there is clinical evidence of deterioration in the condition of these patients. *Gastro-intestinal effects:* In clinical studies, some patients treated with etoricoxib, developed perforations, ulcers or bleeds (PUBs). Independent of treatment, patients with a history of GI perforation, ulcers and bleeding and those aged greater than 65 years are known to be at higher risk of a PUB. *Hepatic effects:* Elevations of ALT and/or AST (>3 times the upper limit of normal) have been reported in approximately 1% of patients treated in trials with etoricoxib 60 mg and 90 mg for up to one year. Monitor any patient with symptoms/signs of liver dysfunction or in whom
an abnormal liver function test has occurred. Discontinue etoricoxib if signs of hep
insufficiency occur, or if persistently abnormal liver function tests (3 times the upper limi
normal) are detected. *General:* Maintain appropriate medical supervision when treating
elderly and patients with renal, hepatic or cardiac dysfunction with etoricoxib. Use caution w
initiating treatment in patients with considerable dehydration. Rehydrate patients prior to star
therapy with etoricoxib. Etoricoxib may mask fever. Use of etoricoxib is not recommende
women attempting to conceive. *Interactions (pharmacodynamic): Oral anticoagulants:* clo
monitor the prothrombin time INR when therapy with etoricoxib is initiated or the dose chan
in patients receiving oral anticoagulants or similar agents, particularly in the first few d
Diuretics and ACE-inhibitors: NSAIDS may reduce the effect of diuretics and antihyperten
drugs. In some patients with compromised renal function, the co-administration of an A
inhibitor and cyclo-oxygenase inhibitors may result in further deterioration of renal funct
which is usually reversible. *Aspirin:* etoricoxib can be used concomitantly with aspirin at d
used for cardiovascular prophylaxis (low dose aspirin). However, concomitant administra
of low dose aspirin with etoricoxib may result in an increased rate of GI ulceration or o
complications compared to use of etoricoxib alone. Concomitant administration of etoric
with doses of aspirin **above** those for cardiovascular prophylaxis, or with other NSAIDS is
recommended. *Cyclosporin/tacrolimus:* monitor renal function when etoricoxib and ei
cyclosporin or tacrolimus is used in combination. *Interactions (pharmacokinetic) The ef*
of etoricoxib on the pharmacokinetics of other drugs: Lithium: the plasma concentratio
lithium is increased by NSAIDS, therefore monitor and adjust blood lithium and lithium dos
if necessary. *Methotrexate:* adequate monitoring is recommended for methotrexate-rel
toxicity when etoricoxib and methotrexate are administered concomitantly. *Oral Contracept*
(OC): Administration of etoricoxib 120 mg with an OC containing 35 mcg ethinyl estra



lammation in a broad range of indications

ARCOXIA®
etoricoxib

) and 0.5 to 1 mg norethindrone for 21 days, either concomitantly or separated by 12 hours, eased the steady state $AUC_{0\text{-}24hr}$ of EE by 50 to 60%; however, norethindrone concentrations erally did not increase to a clinically relevant degree. Consider this increase in EE centration when selecting an oral contraceptive for use with etoricoxib. *Digoxin:* Patients igh risk of digoxin toxicity should be monitored for an increase in digoxin C_{max} when icoxib and digoxin are administered concomitantly. *Effect of etoricoxib on drugs metabolised sulfotransferases:* Etoricoxib is an inhibitor of human sulfotransferase activity, particularly LT1E1 and has been shown to increase the serum concentrations of ethinyl estradiol. It may prudent to exercise care when administering etoricoxib concurrently with other drugs primarily abolised by human sulfotransferases (e.g. oral salbutamol and minoxidil). *Effect of etoricoxib drugs metabolised by CYP isoenzymes:* Based on *in vitro* studies, etoricoxib is not expected nhibit cytochromes P450 (CYP) 1A2, 2C9, 2C19, 2D6, 2E1 or 3A4. In a study in healthy jects, daily administration of etoricoxib 120 mg did not alter hepatic CYP3A4 activity as essed by the erythromycin breath test. *Effects of other drugs on the pharmacokinetics of icoxib:* The main pathway of etoricoxib metabolism is dependent on CYP enzymes. CYP3A4 ears to contribute to the metabolism of etoricoxib *in vivo*. *Ketoconazole:* a potent inhibitor CYP3A4, dosed at 400 mg once a day for 11 days to healthy volunteers did not have any ically important effect on the single-dose pharmacokinetics of 60 mg etoricoxib (43% increase AUC). *Rifampicin:* Co-administration of etoricoxib with rifampicin, a potent inducer of CYP ymes, produced a 65% decrease in etoricoxib plasma concentrations, an interaction which y result in recurrence of symptoms. *Antacids:* Antacids do not affect the pharmacokinetics etoricoxib to a clinically relevant extent. *Pregnancy:* contra-indicated in the first, second third trimesters of pregnancy. *Lactation:* contra-indicated.

SIDE EFFECTS
In clinical studies the following undesirable effects were reported at an incidence greater than placebo in patients with OA, RA or chronic low back pain treated with etoricoxib 60 mg or 90 mg for up to 12 weeks: *[Common (>1/100, <1/10) Uncommon (>1/1000, <1/100) Rare (>1/10,000, <1/1,000)]*
Infections and infestations: *Uncommon:* gastro-enteritis, upper respiratory infection, urinary tract infection. ***Immune system disorder:*** *Very rare:* drug hypersensitivity. ***Metabolism and nutrition disorders:*** *Uncommon:* appetite increase or decrease, oedema/fluid retention, weight gain. ***Psychiatric disorders:*** *Uncommon:* anxiety, depression, mental acuity decreased. ***Nervous system disorder:*** *Common:* dizziness, headache. *Uncommon:* dysgeusia, insomnia, paraesthesia/hypaesthesia, somnolence. ***Eye disorders:*** *Uncommon:* blurred vision. ***Ear and labyrinth disorders:*** *Uncommon:* tinnitus. ***Cardiac disorders:*** *Uncommon:* congestive heart failure, non-specific ECG changes. *Very rare:* myocardial infarction. ***Vascular disorders:*** *Uncommon:* flushing, hypertension. *Very rare:* cerebrovascular accident. ***Respiratory, thoracic and mediastinal disorders:*** *Uncommon:* cough, dyspnoea, epistaxis. ***Gastro-intestinal disorders:*** *Common:* gastro-intestinal disorders (e.g. abdominal pain, flatulence, heartburn), diarrhoea, dyspepsia, epigastric discomfort, nausea. *Uncommon:* abdominal distention, acid reflux, bowel movement pattern change, constipation, dry mouth, gastroduodenal ulcer, irritable bowel syndrome, oesophagitis, oral ulcer, vomiting. *Very Rare:* gastro-intestinal perforation and bleeding. ***Skin and subcutaneous tissue disorders:*** *Uncommon:* ecchymosis, facial oedema, pruritus, rash. ***Musculoskeletal, connective tissue and bone disorders:*** *Uncommon:* muscular cramp/spasm, musculoskeletal pain/stiffness. ***Renal and urinary disorders:*** *Uncommon:* proteinuria. ***General disorders and administration site conditions:*** *Common:* asthenia/fatigue, flu-like disease. *Uncommon:* chest pain. ***Investigations:*** *Common:* ALT increased, AST increased. *Uncommon:* blood urea nitrogen increased, creatine phosphokinase inc haematocrit decreased, haemoglobin decreased, hyperkalaemia, leukocytes decreased, p decreased, serum creatinine increased, uric acid increased. The following serious unde effects have been reported in association with the use of NSAIDs and cannot be ruled etoricoxib: nephrotoxicity including interstitial nephritis and nephrotic syndrome an failure; hepatotoxicity including hepatic failure and jaundice; cutaneo-mucosal adverse and severe skin reactions.

PACKAGE QUANTITIES AND BASIC NHS COST
60 and 90 mg Tablets: packs of 28 tablets £22.96; 120 mg Tablets: packs of 7 tablets

Marketing Authorisation numbers
Tablet 60 mg PL 0025/0422; Tablet 90 mg PL 0025/0423; Tablet 120 mg PL 0025/04

Marketing Authorisation holder
Merck Sharp & Dohme Limited, Hertford Road, Hoddesdon, Hertfordshire EN11 9B
POM **Date of review:** July 2002
® denotes registered trademark of Merck & Co., Inc., Whitehouse Station, NJ, USA.
© Merck Sharp & Dohme Limited 2002. All rights reserved.

MSD
Merck Sharp & Dohme Limited
Hertford Road, Hoddesdon, Hertfordshire EN11 9

NEW BOOKS FROM OXFORD

Oxford Handbook of Anaesthesia

Keith Allman, Consultant Anaesthetist, Royal Devon and Exeter Hospital, and **Iain Wilson**, Consultant Anaesthetist, Royal Devon and Exeter Hospital

- **A new volume in the successful Oxford Handbooks series**
- **Provides practical guidelines for all anaesthetists, from junior to consultant level**
- **The only truly concise yet comprehensive guide to anaesthetic practice**
- **Includes useful appendices - a checklist of anaesthetic apparatus, a drug formulary, and a list of normal values**

A long-awaited new addition to the acclaimed *Oxford Handbooks* series, the *Oxford Handbook of Anaesthesia* is the first truly concise yet comprehensive guide for anaesthetists, providing a practical approach to anaesthetic practice. Written by experts within their fields, the emphasis is on providing clear and reliable advice on a range of surgical situations - advice that can be accessed within seconds. Also included is information on preoperative considerations such as consent, implications of pre-existing medical conditions, postoperative problems, along with a list of anaesthetic drug dosages, infusions, and normal values.

The *Oxford Handbook of Anaesthesia* includes valuable advice for registrars and those sitting exams, whilst also being the one essential book for all anaesthetists, both junior and experienced, to keep in their pockets at all times.

0-19-263273-6, February 2002, £22.95, Flexicovers, 1168 pages, 47 line drawings

The Complete Recovery Room Book

Third Edition

Anthea Hatfield, *Armed Forces Hospital, Riyadh, Kingdom of Saudi Arabia, and* ***Michael Tronson***, *Box Hill Hospital, Melbourne, Australia*

- **A new edition of a highly successful book on caring for patients in the vital hours after surgery**
- **Substantial revisions include new sections on paediatrics, techniques for limiting cross infection, prion disease, HIV and latex allergy, as well as an updated review of drugs used in the recovery room**
- **Heavily illustrated, with clearly presented guidelines**

'The authors have given clear accounts of recovery room care and I am pleased to donate my copy to the recovery room... The layout is imaginative and the book is easy to read. The aphorisms are helpful. There are a number of figures and diagrams, some of which contain guidelines and protocols that could be adapted for wall charts. There are useful appendices, which include information on infusions, arrhythmias, numerical data and emergency trolleys.'
British Journal of Anaesthesia

0-19-263218-3, April 2001, Paperback, 586 pages, numerous line figures, £32.50

Perioperative Medicine

Managing surgical patients with medical problems

Edited by ***Anthony Nicholls***, *Consultant Physician/Nephrologist, Royal Devon and Exeter Hospital, and* ***Iain Wilson***, *Consultant in Anaesthetics and Intensive Care, Royal Devon and Exeter Hospital*

- **Guidelines are concise, didactic, and easily accessible**
- **Essential handbook for junior surgeons and anaesthetists**

"The book succeeds in its aim to provide information and guidance for the clinical management of surgical patients with common medical problems...The information is highly relevant and practical. There is also guidance where more specialist input is considered necessary...In conclusion, Perioperative Medicine *is a pocket reference that contains a wealth of useful information. I would recommend it to all medical staff involved in the perioperative care of patients, and particularly to house staff.'* ***British Journal of Plastic Surgery***

0-19-262975-1, January 2000, Flexicovers, 400 pages, numerous figures and tables, £19.95

ALSO AVAILABLE FROM OXFORD UNIVERSITY PRESS:

An Evidence-based Resource for Pain Relief

H. J. McQuay and R. A. Moore

This book provides a review of clinical trials examining the effectiveness of many of the interventions commonly used in pain relief.

0-19-263048-2, 1998, Paperback, £35.00

Mathematics and Statistics in Anaesthesia

Steven Cruickshank

This book presents simple mathematical ideas and explains how they can be used to model and understand problems which arise in clinical anaesthesia.

1998
0-19-262312-5, Paperback, £27.50
0-19-262313-3, Hardback, £55.00

The Management of Acute Pain

Second Edition

Gilbert Park, Barbara Fulton and Siva Senthuran

This book provides simple, practical guidelines for those who prescribe and administer drugs for acute pain relief.

0-19-262467-9, 2000, Paperback, £21.95

Oxford Handbook of Acute Medicine

Punit S. Ramrakha and Kevin P. Moore

0-19-262682-5, 1997, Flexicovers, £19.95

Oxford Handbook of Critical Care

M. Singer and A. R. Webb

0-19-262542-X, 1996, Flexicovers, £22.95

Ordering books is easy!

UK & Europe:
email book.orders@oup.co.uk
web www.oup.co.uk
tel +44 (0) 1536 454534
fax +44 (0) 1536 454518

USA:
tel (toll free) 1-800-451-7556
fax 1-919-677-1303
email medical@oup-usa.org

For more information on any of these titles or a leaflet containing details of Oxford's other Anaesthesia titles, please email medicine.books@oup.co.uk

OXFORD
UNIVERSITY PRESS

Never miss a twitch?

stones and the oxygen alarm did not sound? If so, please contact:

Dr P. A. Charlebois, 2425 Eglinton Avenue East, Scarborough, Ontario, Canada.

Third Euro-PNB Winter Symposium: postgraduate course on peripheral nerve blockade in surgery and pain management for anaesthesiologists

Excelsior Mila Hotel, Crans-Montana, Switzerland, January 16–19, 2003

Meet European experts in this stimulating course and workshops in an exciting environment.

Registration before December 1, 2002 to: Assoc. Professor Alain Borgeat, Department of Anaesthesia and Intensive Care, Orthopedic University Clinic, Balgrist/Zürich, Forchstrasse 340, CH-8008 Zürich, Switzerland. Tel: +41 1 386 38 32; Fax: +41 1 386 16 09; E-mail: agorgeat@balgrist.unizh.ch

21st Annual Symposium: Clinical Update in Anesthesiology and Advances in Techniques of Cardiopulmonary Bypass with International Faculty and Industrial Exhibits

Antigua, West Indies, January 19–25, 2003

For information on abstracts, posters and free papers (deadline: November 4, 2002) please contact: Helen Phillips, Mount Sinai Medical Centre, 1 Gustave L. Levy Place, Box 1010, NY 10029-6574, USA. Tel: +1 212 241 7467; Fax: +1 212 426 2009; E-mail: helen.phillips@mssm.edu

14th SW Thames Anaesthesia Update

Belle Plagne, French Alps, January 27–31, 2003

The scientific programme will include lectures and discussions on: acute and chronic pain; paediatric update; obstetric anaesthesia; neurology and anaesthesia; ITU and relevant medical topics; cardiothoracic anaesthesia; day case surgery; regional blocks; new drugs update; training and education; clinical governance; information technology; free papers, guest speakers, workshops, videos on new drugs, equipment and techniques.

Open to all anaesthetists. Anaesthetists in training presenting papers are eligible for prizes. Deadline for abstracts: December 10, 2002. Meeting approved for CEPD.

For more information and to secure a place please contact: Dr J. B. Liban, Anaesthetic Department, St George's Hospital, Blackshaw Road, London SW17 0QT. Tel: +44 (0) 208725 0018; Fax: +44 (0) 208725 3135; E-mail: liban@mailbox.co.uk; Website: www.doctorsupdates.com (on-line registration).

10th Annual Paediatric Anaesthesia Update

The Manchester Conference Centre, Manchester, February 14, 2003

For further information, please contact:

The Secretary, University Department of Anaesthesia, Royal Manchester Children's Hospital, Hospital Road, Pendlebury, Manchester M27 4HA, UK. Tel/Fax: +44 (0) 161 727 2291; E-mail: ansecrmch@zoom.co.uk

Legal and Ethical Issues in Anaesthesia and Critical Care

Glenfield Hospital, Leicester, February 21, 2003

For further information, please contact:

Conference Co-ordinator, Clinical Education Centre, Glenfield Hospital, Groby Road, Leicester LE3 9QP, UK. Tel: +44 (0) 116 250 2305; Fax: +44 (0) 116 256 3334; E-mail: jackie.howarth@uhl-tr.nhs.uk

77th Clinical and Scientific Congress of the International Anesthesia Research Society

New Orleans Marriott, New Orleans, Louisiana, March 22–26, 2003

For further information, please contact:

International Anesthesia Research Society, 2 Summit Park Drive, Suite 140, Cleveland, OH 44131-2553, USA. Tel: +1 216 642 1124; Fax: +1 216 642 1127; E-mail: iarshq@iars.org; Website: www.iars.org

Advances in Anatomy and Clinical Examination of the Hand and Wrist

Genval (Brussels), Belgium, March 28–29, 2003

Presymposium Hands-on Course of Hand Surgical Anatomy, March 27, 2003

The symposium will promote exchange between scientists and clinicians, and will include presentations by invited faculty. Participants may submit original papers for a limited number of oral presentations, and there will be considerable time reserved for discussion. Deadline for submission of abstracts: December 31, 2002.

For further details, please contact: F. Schuind, MD, PhD, Department of Orthopaedics, Erasme University Hospital, 808 route de Lennik, B-1070 Brussels, Belgium. Tel: +32 2 555 68 44/36 45; Fax: +32 2 520 35 36; E-mail: Hand.congress@ulb.ac.be

German Congress of Anaesthesiology 2003

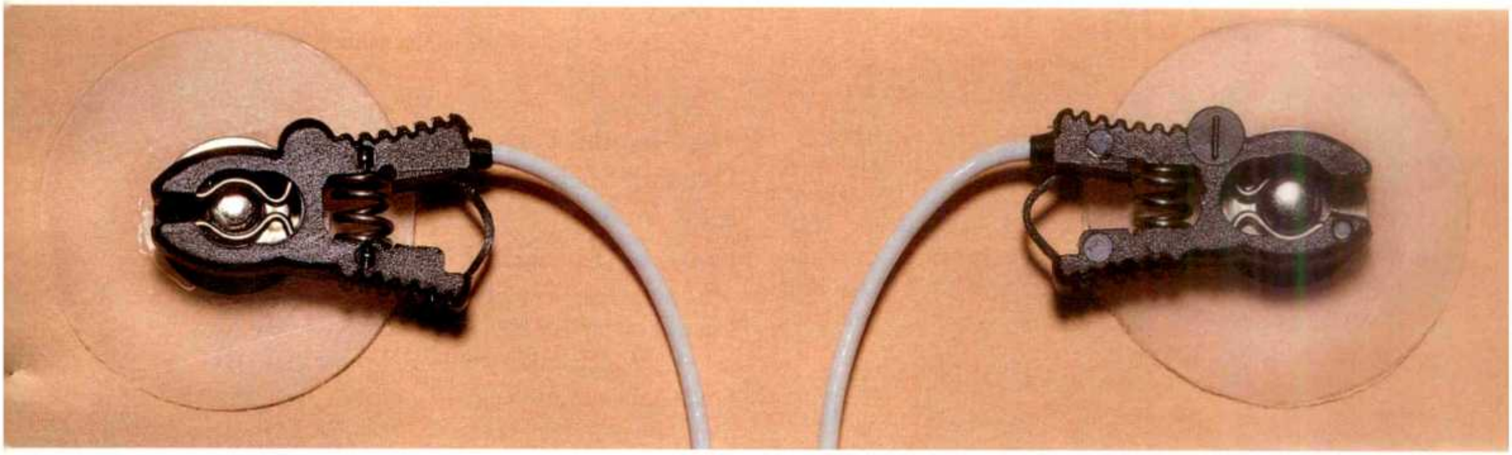
(DAK 2003)

München, April 9–13, 2003

For further information, please contact:

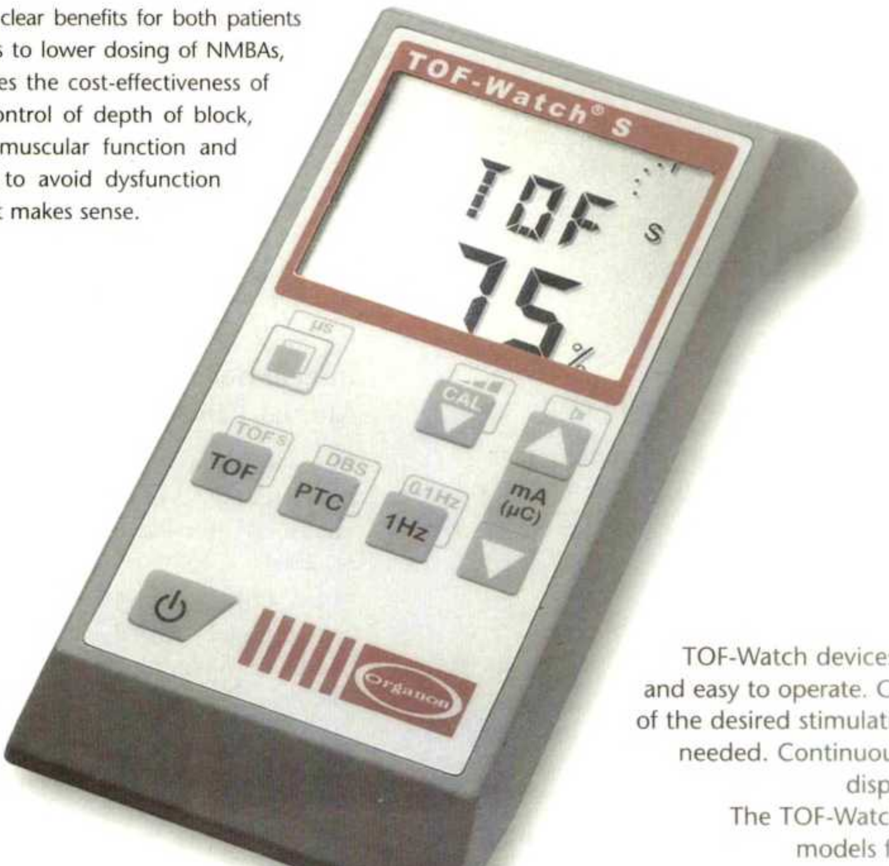
Medizinisch Congressorganization Nürnberg AG.
Tel: +49 911 393160; Fax: +49 911 331204

Objective transmission monitoring



Eyes that never miss a twitch!

Monitoring neuromuscular block has clear benefits for both patients and staff. The TOF-Watch contributes to lower dosing of NMBAs, enhances patient safety and improves the cost-effectiveness of treatment. It also allows optimal control of depth of block, promotes faster recovery of neuromuscular function and spontaneous ventilation and helps to avoid dysfunction resulting from prolonged paralysis. It makes sense.



TOF-Watch
User-friendly operation in routine clinical practice

TOF-Watch S
eatures slow TOF especially suited for use in the Intensive Care Unit

TOF-Watch SX
Designed for scientific use in a GCP setting

TOF-Watch devices are small, lightweig and easy to operate. Calibration and selectio of the desired stimulation mode are all that needed. Continuous monitoring and dat display are fully automati The TOF-Watch range offers differer models for specific application

TOF-Watch®
Safe NMBA-use pays dividends

Organon

For further information, please contact
N.V. Organon, PO Box 20, 5340 BH Oss
The Netherlands, www.organon.com

® indicates trademark(s) registered in one or more countries

International Consensus Conference in Intensive Care Medicine—'Challenges in End-of-Life Care in the ICU'

Brussels, Belgium, April 24–25, 2003

This conference aims to evaluate available scientific knowledge and to advance the understanding of End-of-Life care. The questions to be answered: (i) Is there a problem with End-of-Life care in the ICU?; (ii) What is the 'epidemiology' of death in the ICU?; (iii) Who takes the decision to limit life-sustaining treatments in the ICU?; (iv) What explains the differences between countries and cultures regarding End-of-Life care in the ICU?; (v) What is the optimal care for patients dying in the ICU? Jury will deliberate on April 26–27.

For more information, please contact: ESICM ICC–Mrs Estelle Flament, 40 Avenue Joseph Wybran, B-1070 Brussels, Belgium; Tel: +32 (0)2 559 03 55; Fax: +32 (0)2 527 00 62; E-mail: public@esicm.org; Website: www.esicm.org.

27th Congress of The Scandinavian Society of Anaesthesiology and Intensive Care Medicine

Helsinki, Finland, August 16–20, 2003

A biannually arranged Scandinavian congress in one of the five Scandinavian countries; language: English.

For further information please contact: Prof. Per H. Rosenberg, Helsinki University Hospital, Helsinki FIN00029 HUS, Finland.

E-mail: per.rosenberg@hus.fi
Or: CONGREX/Blue & White Conferences Oy
E-mail: congrex@congrex.fi
Web address: www.congrex.fi

Société Française d'Anesthésie et de Réanimation

Annual congresses will take place in Palais des Congrés, Porte Maillot, Paris on the following dates:

September 18–21, 2003
September 20–October 3, 2004
September 29–October 2, 2005

For further information, please contact: SFAR, 74, rue Raynouard, F-75016 Paris, France. Tel: +33 1 45 25 82 25; Fax: +33 1 40 50 35 22; E-mail SFAR@invivo.edu

Dingle 2003—5th Current Controversies in Anaesthesia and Peri-operative Medicine

Dingle, County Kerry, Ireland, October 1–5, 2003

For further information contact:

Dr Monty Mythen, Director, Centre for Anaesthesia, UCL, Room 103, 1st Floor Crosspiece, Middlesex Hospital, London, W1T 3AA, London, UK. Fax: +44 (0)20 7580 6423; E-mail: uch.acru@btinternet.com

7th Biennial Congress of the Asian and Oceanic Society of Regional Anesthesia and Pain Medicine

Bangkok, Thailand, November 5–8, 2003

A biennial congress with a scientific programme of special lectures, symposiums, and workshops on various techniques of regional anaesthesia and pain medicine.

For further information, please contact: AOSRA Secretariat, 39 Pradipat 10 (Phaholyothin 11) phyathai, Bangkok 10400, Thailand. Tel: +66 0 2615 7301; Fax: +66 0 2615 7309; Mobile: +66 (01) 836 1368; E-mail: cdm@cdmthailand.com

Web address: http://www.cdmthailand.com

13th World Congress of Anaesthesiologists

Palais des Congrès de Paris, Paris, France, April 18–23, 2004

For further details, please contact the Congress Office at: COLLOQUIUM, 12 rue de la Croix Faubin, F-75557 Paris cedex 11, France. Tel: +33 (0) 1 44 64 15 15. Fax: +33 (0) 1 44 64 15 16/17. E-mail: wca2004@colloquium.fr Website: www.wca2004.com

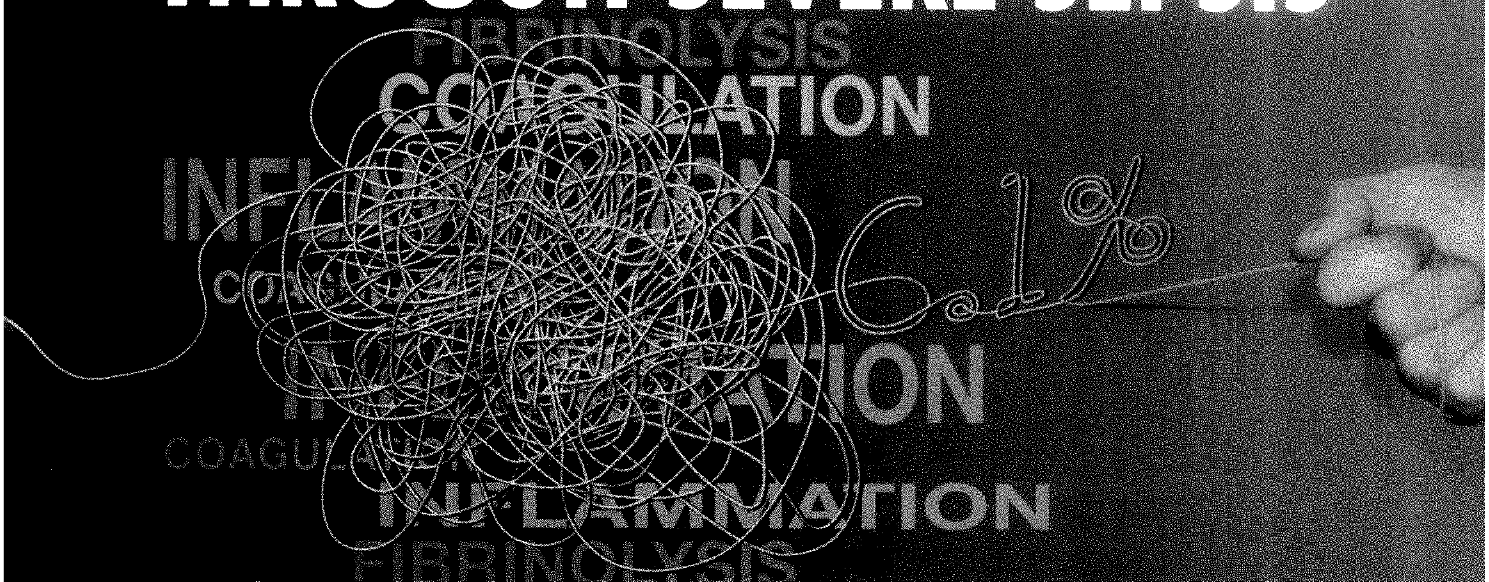
International Anaesthesia Research Society Annual Clinical and Scientific Congresses

78th Clinical and Scientific Congress of the International Anesthesia Research Society, Tampa Marriot Waterside Hotel, Tampa, Florida, March 27–31, 2004

79th Clinical and Scientific Congress of the International Anesthesia Research Society, Hilton Hawaiian Village, Honolulu, Hawaii, March 11–15, 2005

For information please contact: International Anesthesia Research Society, 2 Summit Park Drive, Suite 140, Cleveland, Ohio 44131–2553, USA. Tel: +1 16 642 1124; Fax: +1 216 642 1127; E-mail: iarshq@iars.org; Website: www.iars.org

PULL MORE PATIENTS THROUGH SEVERE SEPSIS



Proven to reduce absolute mortality from 30.8% to 24.7% (by 6.1%) in severe sepsis patients

ABBREVIATED PRESCRIBING INFORMATION XIGRIS* (DROTRECOGIN ALFA [ACTIVATED])

Presentation: Glass vials containing 5 mg or 20 mg drotrecogin alfa (activated) powder for solution for infusion. **Uses:** Xigris is indicated for the treatment of adult patients with severe sepsis with multiple organ failure when added to best standard care. **Dosage and Administration:** Xigris should be prescribed by doctors experienced in the care of patients with sepsis. The recommended dose of Xigris is 24 µg/kg/hr given as a continuous intravenous infusion for a total duration of 96 hours. No dose adjustments required in adult patients with severe sepsis with regard to age, gender, hepatic or renal function. The pharmacokinetics have not been studied in patients with pre-existing end stage renal failure or chronic hepatic disease. **Contra-indications:** Because drotrecogin alfa (activated) may increase the risk of bleeding, Xigris is contra-indicated in the following situations: Active internal bleeding; patients at increased risk for bleeding; platelet count $<30{,}000 \times 10^6$/L, even if the platelet count is increased after transfusions; known bleeding diathesis except for acute coagulopathy related to sepsis; any major surgery; patients with epidural catheter; history of severe head trauma; gastro-intestinal bleeding within 6 weeks; trauma patients at increased risk of bleeding; Patients with intracranial pathology; neoplasm or evidence of cerebral herniation; haemorrhagic stroke within 3 months; A-V malformations; Concurrent heparin therapy ≥ 15 International Units/kg/hr; Chronic severe hepatic disease. Xigris is also contra-indicated in patients with known hypersensitivity to drotrecogin alfa (activated), to any of the formulation excipients, or to bovine thrombin. **Warnings and Special Precautions:** *Bleeding:* Drotrecogin alfa (activated) has the potential to increase the risk of bleeding. In some conditions requiring the recent administration of thrombolytic therapy, oral anticoagulants, aspirin or other platelet inhibitors, or recent ischaemic stroke, the risks of the administration of Xigris should be weighed against the anticipated benefits. For procedures with an inherent bleeding risk, discontinue Xigris for 2 hours prior to the start of the procedure. Xigris may be restarted 12 hours after major invasive procedures. If sequential tests of haemostasis (including platelet count) indicate severe or worsening coagulopathy, the risk of continuing the infusion should be weighed against the expected benefit. Virtually no measurable activity of drotrecogin alfa (activated) is present 2 hours after obtaining a blood sample. **Interactions:** Drug interactions with Xigris have not been studied in patients with sepsis. Caution should be employed when Xigris is used with other drugs that affect haemostasis. *Heparin:* Two-thirds of patients in the Phase 3 trial received prophylactic doses of unfractionated or low molecular weight heparin. There was no observed increase in the risk of bleeding events reported as serious adverse events in drotrecogin alfa (activated) patients receiving prophylactic heparin. **Pregnancy and Lactation:** Xigris should not be used during pregnancy or lactation unless clearly necessary. **Driving, etc:** Not applicable. **Undesirable Effects:** Xigris has the potential to increase the risk of bleeding. In both treatment groups of a Phase 3 clinical trial, the majority of bleeding events were ecchymosis or gastro-intestinal tract bleeding. In the Phase 3 clinical trial, serious bleeding events occurred in 3.5% and 2.0% in drotrecogin alfa (activated)-treated and placebo-treated patients, respectively. In the Phase 3 study, 2 cases of intracranial haemorrhage (ICH) occurred during the infusion period for drotrecogin alfa (activated)-treated patients and no cases were reported in the placebo-treated patients. In non-placebo-controlled trials, ICH has been reported in patients receiving drotrecogin alfa (activated) with an incidence of approximately 0.9% during the infusion period. The risk of ICH may increase with severe coagulopathy and severe thrombocytopenia (see sections 4.3 and 4.4 of the *Summary of Product Characteristics* [SPC]). The incidence of all bleeding events in open clinical trials (during study period) is 6.6%. In the Phase 1 studies, adverse events with a frequency of ≥ 5% included headache (30.9%), ecchymosis (23.0%), and pain (5.8%). *For further information see SPC.* **Legal Category:** POM. **Marketing Authorisation Numbers:** EU/1/02/225/001, EU/1/02/225/002. **Basic NHS Cost:** 1 x 5 mg vial: £152.05; 1 x 20 mg vial £608.19. **Date of Preparation or Last Review:** October 2002. **Full Prescribing Information is Available From:** Eli Lilly and Company Limited, Lilly House, Priestley Road, Basingstoke, Hampshire, RG24 9NL. Telephone: Basingstoke (01256) 315999. *XIGRIS (drotrecogin alfa [activated]) is a trademark of Eli Lilly and Company.

XIG218. October 2002.

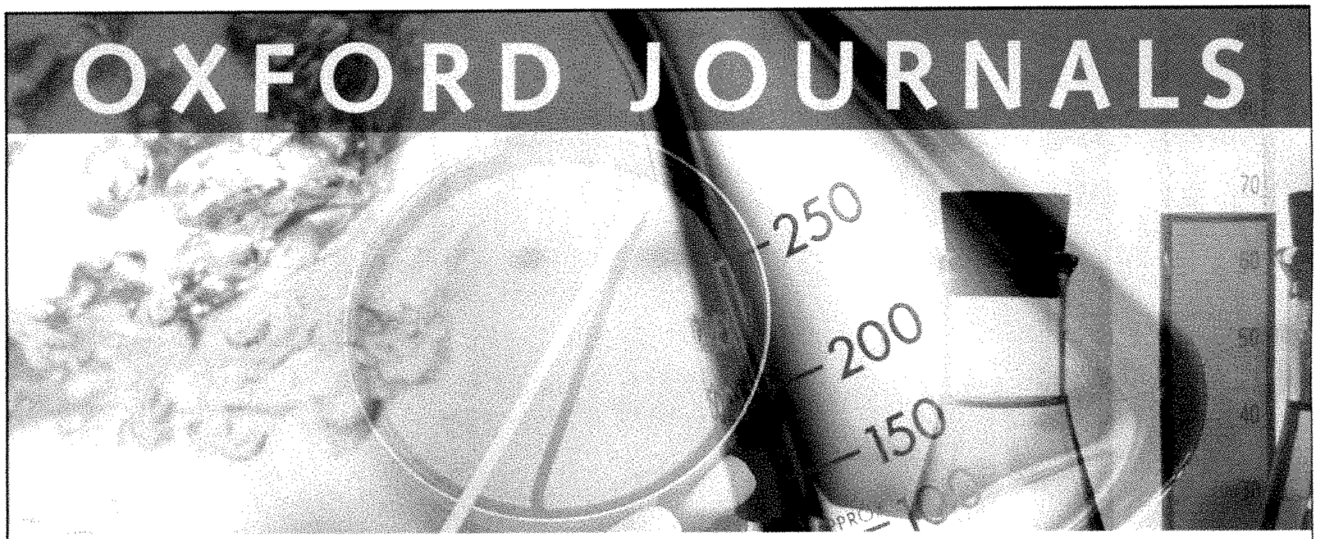
Xigris was proven to reduce absolute mortality in severe sepsis patients from 30.8% to 24.7% in PROWESS, the landmark double-blind, randomised, placebo-controlled, multicentre, international trial (n=1690)[1]. This 6.1% absolute mortality reduction is very favourable when compared to routinely used agents for the treatment of other diseases, such as tPA (1% versus streptokinase in AMI[2]) and streptokinase (2.8% versus placebo in AMI[3]). A recombinant version of a naturally occurring human protein, Xigris improves organ function by the unique combination of its anti-inflammatory, anti-thrombotic and pro-fibrinolytic actions[1].

Add Xigris to your treatment options to help you pull more patients through severe sepsis.

REFERENCES

1. Bernard GR et al. *N Engl J Med* 2001;**344**:699-708. 2. GUSTO Investigators Collaborative Group. *N Engl J Med* 1993;**10**:673-682. 3. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet* 1988;ii:349-360.

Xigris▼
drotrecogin alfa (activated)



OXFORD JOURNALS

Medicine

www.oupjournals.org/medicine/?f2

Oxford University Press publishes some of the most respected and highly-cited medical journals in the world including:

BJA: British Journal of Anaesthesia

Human Reproduction

Journal of Antimicrobial Chemotherapy

Nephrology Dialysis Transplantation

Rheumatology

➲ **FULL TEXT** *now online*

If you are a current print subscriber (institutional or personal), visit **www3.oup.co.uk/Register/?f2** to activate your online access.

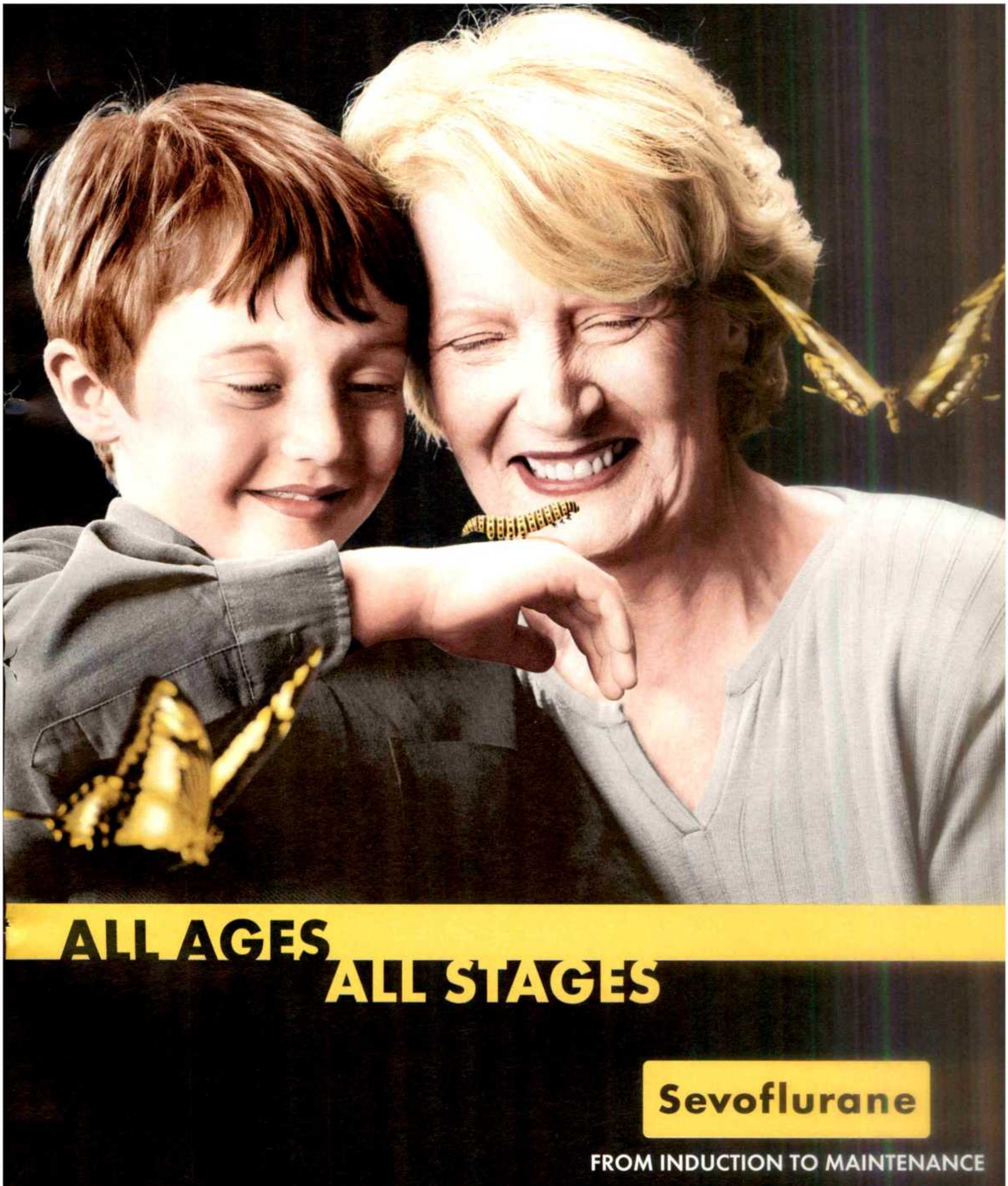
➲ **FREE @ the web site:**

- **tables of contents by e-mail**
- **sample issues**
- **abstracts and tables of contents**
- **instructions to authors**

To subscribe to the above journals, visit the web site @
www.oupjournals.org/medicine/?f2

For further information please contact:
Journals Dept. • E-mail: jnls.cust.serv@oup.co.uk
Tel: +44 1865 267907 • Fax: +44 1865 267835
In the Americas, please contact:
Journals Dept. • E-mail: jnlorders@oup-usa.org
Tel: +1 800 852 7323 (USA/Canada) or +1 919 677 0977
(outside USA/Canada) • Fax: +1 919 677 1714

OXFORD
UNIVERSITY PRESS



Sevoflurane Prescribing Information. Presentation: Amber bottle containing 250ml sevoflurane. **Indications:** For induction and maintenance of general anaesthesia in adult and paediatric patients for inpatient and outpatient surgery. **Dose:** MAC values decrease with age and the addition of nitrous oxide (see Summary of Product Characteristics). *Induction:* In adults up to 5% sevoflurane usually produces surgical anaesthesia in less than 2 minutes; in children up to 7% sevoflurane usually produces surgical anaesthesia in less than 2 minutes. Up to 8% sevoflurane can be used for induction in unpremedicated patients. Maintenance concentrations range from 0.5–3%. *Elderly:* lesser concentrations normally required. **Administration:** Deliver via a vaporiser specifically calibrated for use with sevoflurane. Induction can be achieved and maintenance sustained in oxygen or oxygen-nitrous oxide mixtures. **Contra-indications:** Sensitivity to sevoflurane. Known or suspected genetic susceptibility to malignant hyperthermia. **Precautions:** For use only by trained anaesthetists. Hypotension and respiratory depression increase as anaesthesia is deepened. Malignant hyperthermia. Experience with repeat exposure is very limited. Until further data are obtained, sevoflurane should be used with caution in patients with renal insufficiency. Levels of Compound A (produced by direct contact with CO_2 absorbents) increase with: increase in canister temperature; increase in anaesthetic concentration; decrease in gas flow rate and use of an IV anaesthetic. Sevoflurane metabolism may be induced by CYP2E1 inducers, but not by barbiturates. **Sid**
Dose-dependent cardio-respiratory depression. The type, severity and frequency of adverse events are comparable to those seen
inhalation anaesthetics. Most adverse events are mild to moderate and transient: nausea, vomiting, increased cough, hypotensio
and bradycardia. Hepatitis has been reported rarely. Convulsions may occur extremely rarely, particularly in children. There have
rare reports of pulmonary oedema. As with other anaesthetics, twitching and jerking movements, with spontaneous resolution
reported in children during induction. Patients should not be allowed to drive for a suitable period after sevoflurane a
Use in Pregnancy and Lactation: Use during pregnancy only if clearly needed. It is not known whether sevoflurane is excreted
milk – caution in nursing women. **Overdose:** Stop sevoflurane administration, establish a clear airway and initiate assisted or
ventilation with pure oxygen and maintain adequate cardiovascular function. **Special Storage Conditions:** Do not store ab
Do not refrigerate. Keep cap tightly closed. **Legal Category:** POM **Marketing Authorisation Number:** PL 0037/02
NHS Price: 250ml bottle £123.00. Further information is available on request from Abbott

ABBOTT ANAES

She doesn't just see a monitor.
She sees a better way to deliver patient care.

Take a look at the new Philips IntelliVue Patient Monitoring System with portal technology. It gives clinicians unprecedented access to the patient information they need at the point of decision and on a single screen. The result: less time searching for X-rays, lab results and patient records, and more time to care for patients. To learn more visit www.medical.philips.com/intellivue.

Presenting IntelliVue™

World-class measurements for increased confidence.

Portal technology allows earlier intervention.

Tailored displays support workflow.

PHILIPS

Let's make things better.

BJA

"I would have everie man write what he knowes and no more."—Montaigne

BRITISH JOURNAL OF ANAESTHESIA

Volume 89, Number 6, December 2002

Editorial I

Confidence in statistical analysis

In this era of evidence-based medicine, randomized controlled trials are crucial sources for making clinical decisions. But what should we expect from a randomized controlled trial? First of all, we would like to know if there is a difference between treatments—for example, if a new drug is better than an old one. As we cannot obtain data from the entire population, we set up a randomized controlled trial on a sample of subjects and apply each treatment to a different group. We will almost certainly find some difference between the groups, because even if the same treatment had been applied to both groups we would be very likely to have some difference because of the variability between subjects in their response to the treatment. So, how do we know whether the observed difference is a reflection of a systematic difference in the population as a whole or just a reflection of patient variability? This is usually answered by using a hypothesis test. The way of proceeding is to set up a null hypothesis—that there is no difference between groups. We can calculate a probability (P value) that the observed difference arose only by chance from the variability between patients. For example, if P=0.04, this means that there is a 4% probability that the observed difference is due to chance, and therefore a 96% probability that the alternative hypothesis (there is a difference in the population) is true. The difference observed in any trial is usually regarded as statistically significant when P<0.05 (or sometimes <0.01).

Once we have learnt that there is a significant difference between groups, we would like to know how large the difference is. The difference can be estimated (point estimate) by simply calculating the difference between the mean responses in the two groups. Suppose in one study of 20 patients the mean consumption of morphine during the postoperative period was 30 mg in the control group, in which a conventional analgesic was given during anaesthesia, and 20 mg in the study group, in which a new drug was used. The difference between groups is calculated to be 10 mg.

Next, we recognize that, because we have studied only a sample of subjects, the true difference in the population will probably be a bit bigger or smaller than our point estimate. Therefore we would like to know how much bigger or smaller the true difference might probably be. Hypothesis tests do not quantify this. Most probably as a result, clinicians have tended to ignore this important question of the magnitude of the difference between groups (how much better is the new drug than the old one?) and simply consider whether 'there is a difference' or 'there is no difference'. In fact, we can calculate a range of values that will, with high probability (commonly 95%, less often 99%), contain the true difference in the population. This range of values is called the confidence interval.

The main purpose of the confidence interval is to indicate the (im)precision of the point estimates of population values.[1] More exactly, in a statistical sense, the confidence interval means that if a long series of identical studies were carried out on different samples from the same population and a 95% confidence interval for the difference between groups calculated in each study, then, in the long run, 95% of these confidence intervals would include the population difference. In the study mentioned above, the 95% confidence interval for the difference in the postoperative morphine consumption between groups is calculated to be 2–18 mg. This indicates that the true difference should be, with 95% certainty, somewhere between these values. In other words, the true difference may be as low as 2 mg or as high as 18 mg.

The variability of the subjects studied and the sample size affect the width of the confidence interval: the greater the variability of subjects studied, or the smaller the sample size, the wider the interval. Suppose a study similar to the above was done, but in 200 patients, and that this study again showed the difference in the postoperative morphine consumption between groups to be 10 mg (with similar variability between patients). If the 95% confidence interval for the difference were 2–18 mg for the study of 20 patients, calculation would show it to be 8–12 mg for the study of 200 patients. Therefore, the precision of a point estimate is indicated by the width of the confidence interval: the narrower the interval the more precise the point estimate of the population difference.

There is a close link between the confidence interval and the hypothesis test. When the 95% confidence interval does not contain 0, there is a significant difference (P<0.05), whereas when the interval contains 0 there is no significant difference between groups. Thus, the confidence interval

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

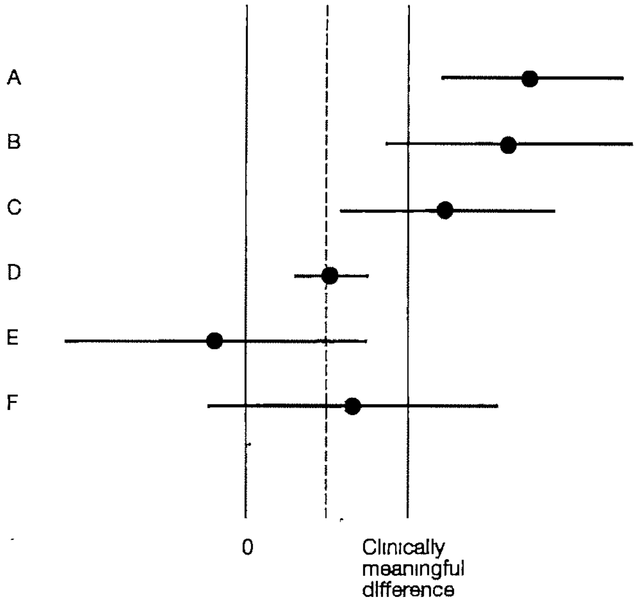


Fig 1 Examples of confidence intervals in relation to zero difference and a proposed clinically meaningful difference. The dashed line indicates half the proposed clinically meaningful difference (see text for details)

allows readers to assess whether or not the difference between groups is statistically significant.

Over the last few decades, statistical analysis has increasingly been used in medical studies. Nevertheless, it is a pity that hypothesis tests have been used predominantly and the usefulness of the confidence interval—another major statistical analysis—has not been well appreciated. In addition, the hypothesis test has often been misused and misinterpreted. Even now, it often appears that the main purpose of studies is to obtain $P<0.05$: P values less than 0.05 are regarded as meaningful and publishable in medical journals, whereas values equal to or greater than 0.05 are considered meaningless and not publishable. However, suppose two new drugs (A and B) have recently been developed and one study showed that drug A was significantly better than the old drug ($P=0.048$), whereas another study showed that there was no significant difference between drug B and the old drug ($P=0.052$). Should we then consider using drug A, but never drug B? The answer should be no. Similarly, both $P=0.053$ and $P=0.12$ are judged as non-significant, but the meaning of these can be quite different. Such dichotomy (significant and non-significant, yes and no, black and white) can produce publication bias and can lead to an unsound clinical judgement.

What we should not forget is that a significant difference between groups does not necessarily mean that there is a clinically meaningful difference. Conversely, a non-significant difference between groups does not necessarily mean that there is no clinically meaningful difference. Why? It is because, in hypothesis testing, a difference which is too small to be clinically meaningful can be statistically significant when a large number of subjects has been studied, whereas a clinically meaningful difference may be non-significant if the number of subjects studied was too small.

Then how can we decide the number of subjects that is appropriate for testing the hypothesis? To do this, it is mandatory to decide, before the start of the study, the minimum true difference between groups that we can regard as clinically meaningful. The number of subjects required is calculated on the basis of the proposed clinically meaningful difference and the anticipated variability of the data. This calculation is called power analysis. Without this calculation, reliable conclusions cannot be drawn from the P values. In particular, when the P value turns out to be $\geqslant 0.05$ (or $\geqslant 0.01$), the hypothesis test indicates a non-significant difference, even though there may in fact be a meaningful population difference (false negative, type II or beta error).[2]

Even if the required number of subjects is calculated correctly, there are still two dangers. First, a statistically significant result may not be genuinely clinically meaningful. For instance, suppose a group of researchers studying a new but expensive antihypertensive drug considered that a decrease in arterial pressure by 10 mm Hg (compared with the placebo group) would be clinically meaningful. Other clinicians might consider that the reduction needed to be 20 mm Hg to be clinically meaningful. The researcher would study a large number of subjects and may achieve a significant difference, even if the drug in fact reduces the blood pressure by only 10 mm Hg. Therefore, this study may not be useful, since clinicians would not use such an expensive drug with a weak effect in daily practice. Secondly, a statistically non-significant result may conceal a meaningful difference. Suppose another group of researchers, studying the same drug, decided that only a decrease of 30 mm Hg was clinically meaningful. They would study a much smaller number of patients so that, if the population difference was only a little larger than the 20 mm Hg that other clinicians considered meaningful, they might report a non-significant result, thereby perhaps inappropriately discouraging clinicians from using the new drug.

Therefore, the implications of a hypothesis test depend on the investigators' opinion of the clinically meaningful difference and thus the test is, in a sense, subjective. This is why it is important that the authors should state unambiguously the null hypothesis and a proposed clinically meaningful difference, to allow readers to assess to what extent the significant or non-significant difference supports or refutes the existence of a difference which they would regard as clinically meaningful. In this sense, the hypothesis test should not, in principle, be used for unplanned comparisons (such as an unexpected difference) where there is no clear null hypothesis.

The confidence interval solves the problems associated with hypothesis tests in several ways. First, the confidence interval facilitates the distinction between a significant

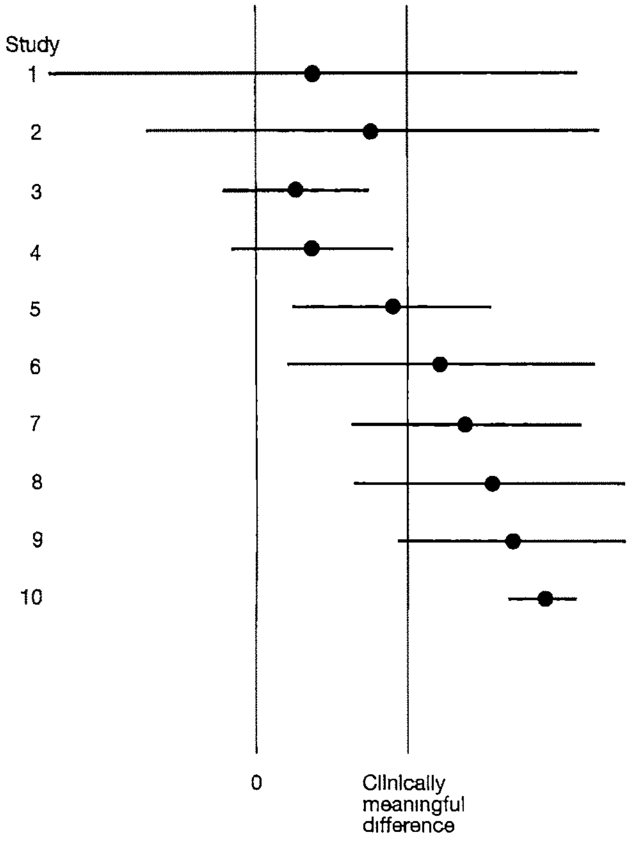


Fig 2 Examples of point estimates with their confidence intervals in relation to zero difference and a proposed clinically meaningful difference

difference and a clinically meaningful difference. There are several possible confidence intervals in relation to a clinically meaningful difference and zero difference between groups (Fig. 1). In Figure 1, hypothesis tests would show significant differences for examples A, B, C and D. In contrast, the confidence intervals indicate that only in example A is the difference almost certainly clinically meaningful. For example B, the difference is likely to be clinically meaningful, but it may not be. For example C, the difference could be clinically meaningful but is doubtful. Lastly, for example D, the confidence interval would indicate that the difference is almost certainly not clinically meaningful.

Secondly, because the confidence interval does not require a particular hypothesis, the results will not be directly affected by the clinically meaningful difference proposed by the researchers. Therefore, by using their own values for the smallest clinically meaningful difference, readers can interpret whether or not the study indicates a difference which they would regard as clinically meaningful. For example, if readers consider that the minimum clinically meaningful difference is half the proposed value in Figure 1 (dotted line), examples A–C can be regarded as showing almost certainly a clinically meaningful difference (because the lower limit is now greater than the smaller proposed value), whereas example D may or may not be clinically meaningful.

Thirdly, the confidence interval may differentiate between no clinically meaningful difference and a beta error In examples E and F, the hypothesis tests would indicate no significant difference between groups. The confidence interval indicates that in example E there would be no clinically meaningful difference between groups, as the upper limit of the interval is less than the value for the clinically meaningful difference. For example F, the confidence interval cannot differentiate between zero difference and a clinically meaningful difference between groups. This is most likely to occur when the number of subjects studied is too small. Nothing can be inferred from this study, which would give a false impression of the absence of an effect (beta error).

Lastly, the confidence interval is potentially useful in examining results from several similar studies. Suppose 10 studies (of various numbers of patients) have been carried out comparing the efficacy of a new drug with that of an old one (Fig. 2). When we examine the results of hypothesis tests, we will find it difficult to draw a conclusion about whether the new drug is clinically more useful than the old one, as six studies (studies 5–10) showed significant differences whereas the other four (studies 1–4) showed non-significance. We may hope to reach a conclusion by repeating similar studies, but this would often aggravate the inconsistencies between studies because, as the number of studies increases, the risk of false-positive and false-negative results also increases. The confidence interval may shed a quite different light. From Figure 2, we can deduce that studies 1 and 2 are useless, since their confidence intervals contain both zero difference and the clinically meaningful difference. Only two of the remaining eight studies (studies 3 and 4) contain zero difference, and the negative segments of the confidence intervals of these two studies are much smaller than the positive segments. In eight of the 10 studies, the confidence interval contains (or exceeds) the value for a clinically meaningful difference, and in five studies the point estimates are greater than the clinically meaningful difference. By seeing these, we can conclude that the new drug is very likely to be genuinely more effective and is likely to produce a clinically meaningful difference in the population at large. In addition. if a new trial of a large number of subjects is done (such as study 10 in Fig. 2), the confidence interval will be narrower than others so that more weight can be given to such a study than to others. Therefore, by examining the degree of difference in each study, and the confidence intervals, we can summarize all the studies. Thus, increasing the number of studies would help us to reach a more reliable conclusion. The most effective way of analysing randomized controlled trials using this concept is by meta-analysis.[3]

Taking these considerations together, the following recommendations can be made. First, authors should state unambiguously a null hypothesis and their proposed value for the clinically meaningful difference (as well as the estimated variability between patients). The excessive use of hypothesis testing should be avoided not only because multiple testing increases the risk of false-positives (alpha error), but also because it is usually unreasonable to produce multiple hypotheses from a single study. Secondly, authors should calculate, before the start of the trial, the number of subjects required (and show the calculation in the Method section), to reduce the risk of a beta error to an acceptable level, such as 5 or 10% (corresponding to a power of 0.95 and 0.9 respectively). Thirdly, the authors should state the point estimate and its confidence interval. Finally, regardless of the presence or absence of a significant difference between groups, efforts should be made to clarify the likelihood of a clinically meaningful difference.

Gardner and Altman[4] have formulated a policy for the *British Medical Journal* that confidence intervals, if appropriate to the type of study, should be used for major findings in both the main text of a paper and its abstract. The *British Journal of Anaesthesia* states in its Guide to Contributors that 'Confidence intervals provide a more informative way to deal with a significance test than a simple *P* value'.[5] Hypothesis tests answer these questions only partially, and the *P* value in itself does not tell us if there is a clinically meaningful difference between groups. Therefore, authors submitting manuscripts to this journal are strongly encouraged to show the confidence interval, at least for the main findings (and perhaps even more so for any supplementary findings), to permit the drawing of a reliable clinical inference.

T. Asai
Department of Anaesthesiology
Kansai Medical University
Osaka 570-8507
Japan
E-mail: asait@takii.kmu.ac.jp

Acknowledgement. I thank Professor Emeritus W. W. Mapleson for his helpful comments on the manuscript.

References

1 Gardner MJ, Altman DG. Estimating with confidence. In: Altman DG, Machin D, Bryant TN, Gardner MJ, eds. *Statistics with Confidence: Confidence Intervals and Statistical Guidelines* London: BMJ Books, 2000; 3–5

2 Yentis SM. The struggle for power in anaesthetic studies. *Anaesthesia* 1996: **51**: 413–4

3 Altman DG. Clinical trials and meta-analyses. In. Altman DG, Machin D, Bryant TN, Gardner MJ, eds. *Statistics with Confidence: Confidence Intervals and Statistical Guidelines*. London: BMJ Books, 2000; 120–138

4 Gardner MJ, Altman DG. Confidence intervals rather than P values: estimation rather than hypothesis testing. *Br Med J* 1986; **292**: 746–50

5 *British Journal of Anaesthesia* Extended guide to contributors. *Br J Anaesth* 2000; **84**: 131–7

Editorial II

Why does smoking protect against PONV?

Postoperative nausea and vomiting (PONV) are among the most common and feared postoperative complications and can occur after both general and regional anaesthesia. Many adults find PONV more distressing than postoperative pain.[1] Over the last decade, there has been some improvement in the understanding of the aetiology, and pathophysiology of PONV and, together with the introduction of new and effective antiemetics there has been some progress into finding a solution to the problem. Unfortunately, however, PONV, which has been described by Kapur as 'the big, little problem',[2] remains an unpleasant and sometimes intractable side-effect, which continues to challenge and frustrate anaesthetists. In today's world of cost-effective medicine, where there are ever-increasing pressures to avoid even minor side-effects of treatment, there has been an explosion of papers on the subject in which every aspect of risk, prevention, anaesthetic technique, and management strategies have been examined. PONV has also been the subject of a recent 1-day symposium organized by The Royal College of Anaesthetists.[3]

Several authors have attempted to categorize PONV in terms of surgical, anaesthetic, non-anaesthetic, and postoperative factors.[4 5] A number of factors have emerged which are associated with the problem. These include age, sex, history of motion sickness, previous PONV, duration and type of surgery, pre-anaesthetic medication, the use of nitrous oxide, facemask ventilation, the use of opiates, early postoperative ambulation, the timing of oral intake, and postoperative pain. Clearly, there are an infinite number of permutations that may lead to an unfavourable outcome. For this reason, there have been attempts to define those variables and in particular, those fixed patient factors that may be used to quantify more meaningfully the extent to which an individual may be at risk. It is also important to take cognisance of these factors in the design of studies of PONV in order to avoid bias. In 1993, Palazzo and Evans[6] studied prospectively 147 patients undergoing minor orthopaedic surgery, by logistic regression analysis, to determine the association of independent fixed patient factors with the incidence of PONV. This study identified history of PONV, sex, and postoperative opioid administration as important factors. A history of motion sickness was weakly associated. There was also an interaction between sex and history of motion sickness. In 1998, Apfel and co-workers,[7] also using stepwise forward logistic regression analysis analysed 1137 patients and identified age, sex, history of PONV or motion sickness, duration of surgery, and *non-smoking* as important risk factors in the aetiology of PONV. Simultaneously, Hough[8] coincidentally identified smoking as a protective factor against PONV. This was confirmed by Chimbira[9] in a larger follow-up study.

Why should cigarette smoking confer protection against PONV? One explanation for such an effect would be the presence of an antiemetic substance in tobacco smoke. The pharmacological receptors which mediate PONV are known to act at the dopamine (D2), cholinergic, histamine (H1), 5-HT3 and NK1 receptors,[10] and if there were an antemetic in cigarette smoke it would have to belong to one of these classes of receptor-blocking drugs. Presumably, if this were the case, then other dopaminergic, cholinergic, or histaminergic effects would occasionally be seen. So far this hypothesis has not borne fruit. Alternatively, the reduction in PONV may be seen as an adaptive response to a repeated emetic stimulus, although it is clear that usually only the uninitiated or those who have consumed excessive amounts find tobacco emetogenic.

Cigarette smoke is a complex mixture of gaseous and particulate material. The gaseous portion, which comprises 60% of tobacco smoke, contains formaldehyde, carbon monoxide, nitric oxide, hydrogen cyanide, and other components.[11] The remaining 40% is the particulate phase. There are about 3500 different substances, which have been isolated in the particulate phase, the principal one of which is the alkaloid, nicotine. Other alkaloids include nornicotine, antabine, and anabasine. There are also acids, including lactones, aldehydes, ketones, alcohols, polyphenols, nitrosamines, and polyaromatic hydrocarbons.[12] The particulate phase minus the alkaloids and water is called tar.

Tar, otherwise known as cigarette smoke condensate (CSC), is a mixture of polycyclic aromatic hydrocarbons (PAHs), *N*-nitrosamines, and aromatic amines.[13] PAHs are the products of incomplete combustion of organic matter such as wood, oil, tobacco, and coal. In recent years, research has focussed to a large extent on these substances, primarily because of their tumorigenic activity and also because they are capable of influencing the activity of hepatocellular enzymes.[14] Examples of the PAHs, which are found in CSC include naphthalene, phenanthrene, anthracene, benzanthracene, pyrene, benzpyrene, and benzfluoranthene.

Detoxification of most drugs occurs via the P450 (CYP) enzyme pathways. In man, the CYP isoenzymes, which are responsible for drug metabolism belong to families 1–4. Of these families, 1–3 are the most important. It has been estimated that 90% of drug and xenobiotic metabolism can be attributed to six enzymes: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4.[15] The purpose of this multienzyme system, which has evolved over millennia in plants and animals, is an evolutionary consequence of plant–animal warfare. Plants synthesized chemicals for self-protection, and animals had to develop xenobiotic-metabolizing enzymes such as cytochrome P450 for the detoxication of these chemicals.[16] It can now be considered as an adaptive response to environmental challenges, in that exposure to a toxic or noxious substance results in the expression of enzymes responsible for the metabolism of the particular toxin. For the most part this is a beneficial response, but it may also result in the formation of a metabolite that is either pharmacologically active or even carcinogenic.[17] When enzymes are induced, dramatic effects on drug clearance and half-life can also occur.

Cigarette smoking can result in as much as a 3-fold increase in CYP1A2 activity from induction by PAHs. CYP1A2 is the major enzyme involved in the metabolism of a number of drugs, some of which are commonly used by anaesthetists. This leads to increased rates of metabolism of these substances, which may lead to an increased dosage requirement.[15] For example, it has been shown that the clearance of theophylline is significantly increased in smokers and that its half-life is decreased by a factor of two.[18] Cessation of smoking can lead to rapid accumulation which necessitates dose readjustment.[19] The metabolism of a number of psychoactive drugs also dependent on CYP1A2 is similarly affected. These include the antidepressives amitriptyline, clomipramine and fluvoxamine, the antipsychotics chlorpromazine and haloperidol, and some anxiolytics such as diazepam and chlordiazepoxide.[20] Of interest to anaesthetists is the increased requirements for analgesia among smokers and the increased metabolism of morphine and meperidine.[21 22] Pentazocine and dextropropoxyphene which are associated with the genesis of PONV may be similarly affected.[23 24]

In contrast, volatile anaesthetics are metabolized by CYP2E1,[25–27] which is also induced by nicotine and PAHs.[18] In a recent study, Apfel and co-workers[28] have demonstrated that volatile anaesthetics are the main cause of PONV within the first two postoperative hours, when pharmacokinetic effects are most likely to account for any perceived differences in recovery. A patient whose liver enzymes, in particular CYP2E1, have been induced as a result of smoking would be expected to have a correspondingly higher rate of metabolism of the respective volatile agent. Such a patient might have a quicker and smoother recovery from anaesthesia.

Our understanding of liver enzymes and how they may be influenced by foreign substances has improved considerably over the last decade and has been the subject of several reviews.[29 30] Liver enzymes are induced or inhibited by a number of commonly used drugs, environmental chemicals, for example insecticides, petroleum products and solvents, as well as foodstuffs, which may therefore interfere with recovery from anaesthesia.

There are a number of well-known serious pharmacological interactions, which occur as a result of P450 inhibition. For example, cimetidine, which is a non-specific inhibitor of several CYP isoenzymes, can interfere with the breakdown of a number of substances including non-depolarizing muscle relaxants,[31] and warfarin,[32] leading to prolonged paralysis and excessive anticoagulation respectively. Another potentially fatal interaction, caused by a cardiac dysrhythmia, is that involving the macrolide antibiotic, erythromycin, which inhibits CYP3A4, and the commonly used antihistamine, terfenadine.[33] The combined use of these two substances can lead to prolongation of the QT interval thereby triggering a specific arrhythmia known as *torsade de pointes*. An identical problem results when excessive amounts of grapefruit juice are consumed while taking terfenadine.[34] Grapefruit juice is known to contain the bioflavanoid, naringin. These bioflavanoids are a group of naturally occurring substances which are thought to be responsible for inhibiting CYP3A4,[35] which is also responsible for metabolizing benzodiazepines and opioids such as alfentanil.[15] Of interest has been the recognition of the ability of these substances also to block enzymes of the CYP2 family.[36] On the other hand, cruciferous vegetables such as cabbage, brussel sprouts, and cauliflower, contain indole-3-carbinole which is a potent inducer of CYP1A2,[37] but they also contain phenethyl isothiocyanate which is an inhibitor of CYP2E1.[16] Another inhibitor of CYP2E1 is dihydrocapsaicin which is found in red peppers.[38] A subject undergoing anaesthesia having recently consumed large amounts of this substance may have an unexpectedly long recovery and if also a smoker may lose his protection against PONV.

Alcohol intake before an anaesthetic is also a hitherto underestimated factor, which probably is as important as tobacco in determining the risk of PONV. Not only is alcohol a potent inducer of CYP2E1, significant increases in the enzyme appearing after only a single ingestion,[38] but there is a curious synergy between alcohol and tobacco. The incidence of alcoholism is 10 times more likely in smokers[39] consistent with the concept that smoking increases ethanol consumption.[40] It would be interesting to speculate that hitherto disregarded patient factor for PONV might be dietary preference and alcohol intake on the evening before surgery.

Liver enzyme status may be subject to genetic polymorphism, with the expression of a number of liver enzymes being dependent on factors such as sex and racial differences. For example, the activity of CYP2D6 (debrisoquine 4-hydroxylase) which is responsible for the metabolism of many drugs, including some opiates, such as codeine,[15 30] which are known to cause PONV, varies widely along racial lines. The prevalence of the poor metabolizer approaches 10% among Caucasians but is virtually zero in Japanese subjects.[41] The breakdown of nicotine is determined by the level of CYP2A6 (coumarin-7-hydroxylase), the activity of which is also determined to some extent by genetic background.[42] CYP2E1 may also be subject to genetic polymorphism,[43] which could explain interindividual differences in the tolerance to anaesthetic agents. Finally, an interesting cause of CYP2E1 induction is obesity,[44] which might also therefore confer resistance to PONV. It might explain the association between halothane hepatitis and obesity,[45] which is known to occur as a result of a reaction to a trifluoroacetyl metabolite of halothane.[46]

In summary, enzyme induction is an important mechanism that may influence the breakdown of a number of volatile and non-volatile anaesthetic agents. The extent to which liver enzymes are induced will determine the rate and possibly the quality of recovery. There are interindividual, racial, and sex-related differences in the activity of liver enzymes including CYP2E1, and this could explain some of the differences in recovery from anaesthesia. There are a number of pharmacological, dietary, and environmental substances including cigarette smoke that can induce or inhibit CYP1A2 and CYP2E1. The way in which an individual responds to an anaesthetic will depend on a subtle interaction of his or her genotype together with these exogenous factors. A novel approach to improving outcome after anaesthesia may be by targeting enzymes pre-emptively with specific inducers to alter their activity and thereby mimic the apparent advantage of the smoker without running the other risks to which he is exposed.

B. P. Sweeney
Poole and Royal Bournemouth Hospitals
Department of Anaesthesia
Royal Bournemouth Hospital
Castle Lane East
Bournemouth
Dorset BH7 7DW
UK
E-mail: bpsween@aol.com

References

1 Koivuranta M, Laara E, Snare L Alahuhta S. A survey of post operative nausea and vomiting. *Anaesthesia* 1997; **52**: 443–9
2 Kapur PA The big, little problem. *Anesth Analg* 1991; **73**: 243–5
3 *Key Advances in the Effective Prevention and Management of Post-operative Nausea and Vomiting*. London: Aeculapius Press, 2002
4 Watcha MF, White PF. Post operative nausea and vomiting: its etiology, treatment and prevention. *Anaesthesiology* 1992; **77**: 162–84
5 Lerman J. Surgical and patient factors involved in post operative nausea and vomiting. *Br J Anaesth* 1992; **69** (Suppl. 1): 24S–32S
6 Palazzo M, Evans R. Logistic regression analysis of fixed patient factors for post operative sickness: a model for risk assessment. *Br J Anaesth* 1993; **70**: 135–40
7 Apfel CC, Greim A, Haubitz I, et *al*. A risk score to predict the probability of post operative vomiting in adults. *Acta Anaesthesiol Scand* 1998; **42**: 495–501
8 Hough MB, Sweeney BP. The influence of smoking on post-operative nausea and vomiting. *Anaesthesia* 1998; **53**: 932–3
9 Chimbira W, Sweeney BP. The effect of smoking on post-operative nausea and vomiting. *Anaesthesia* 2000; **55**: 540–5

10 Hefferman AM, Rowbotham DJ. Post-operative nausea and vomiting—time for balanced antiemesis? *Br J Anaesth* 2000; **5**: 675–7

11 Kilburn KH. Effects of tobacco smoke on biological systems. *Scand J Resp Dis* 1974; **91**: 63–78

12 Severson RF, Snook ME, Arrendale RF, Chortyk OT. Gas chromatographic quantitation of polynuclear hydrocarbons in cigarette smoke. *Analyt Chem* 1976; **48**: 1866–72

13 Schumacher JN, Green CR, Best FW, Newell MP. Smoke composition. An extensive investigation of the water-soluble portion of cigarette smoke. *J Agric Food Chem* 1977; **25**: 310–20

14 Conney AH. Induction of microsomal enzymes by foreign chemicals and carcinogenesis by polycyclic aromatic hydrocarbons. G. H. A. Clowes memorial lecture. *Cancer Res* 1982; **42**: 4875–917

15 Tanaka E. Clinically important pharmacokinetic drug–drug interactions: role of cytochrome P450 enzymes. *J Clin Pharm Ther* 1998; **23**: 403–16

16 Yang CS, Brady JF, Hong JY. Dietary effects on cytochromes P450, xenobiotic metabolism and toxicity. *FASEB J* 1992; **6**: 737–44

17 Wolf CR, Mahmood A, Henderson CJ, *et al.* Modulation of the cytochrome P450 system as a mechanism of chemoprotection. *Int Agency Res Cancer Sci Pub* 1996; **139**: 165–73

18 Zevin S, Benowitz NL. Drug interactions with tobacco smoking. *Clin Pharm* 1999; **36**: 425–38

19 Lee B, Benowitz NL, Jacob WP. Cigarette abstinence, nicotine gum, and theophylline disposition. *Ann Intern Med* 1987; **106**: 553–5

20 Desai HD, Seabolt J, Jann MW Smoking in patients receiving psychotropic medication. *CNS Drugs* 2001; **15**. 464–94

21 Miller LG Cigarettes and drug therapy. pharmacokinetic and pharmacodynamic considerations. *Ther Rev* 1990, **9**: 125–35

22 Ali B, Kaur S, Kumar A, Bhargova KP. Comparative evaluation of stimulatory effects of oral tobacco on nicotine consumption on hepatic microsomal *N*-demethylation. *Biochem Pharm* 1980; **29**. 3087–92

23 Keeri-Szanto M, Pomeroy JR. Atmospheric pollution and pentazocine metabolism. *Lancet* 1971; **1**: 947–9

24 Schein JR. Cigarette smoking and clinically significant drug interactions *Annal Pharmacother* 1995; **29**: 1139–47

25 Kharasch ED, Hankins DC, Cox K. Clinical isoflurane metabolism by cytochrome P450 2E1. *Anaesthesiology* 1999; **90**: 766–71

26 Kharasch ED, Thummel KE. Identification of cytochrome P450 2E1 as the predominant enzyme catalysing human liver microsomal defluorination of sevoflurane, isoflurane and methoxyflurane. *Anaesthesiology* 1993; **79**· 795–807

27 Spracklin DK, Hankins DC, Fisher JM, Thummel KE, Kharasch ED. Cytochrome P4502E1 is the principle catalyst of human oxidative halothane metabolism *In vitro*. *J Pharmacol Exp Ther* 1997; **281**: 400–11

28 Apfel CC, Kranke P, Katz MH, *et al.* Volatile anaesthetics may be the main cause of early but not delayed postoperative vomiting. a randomised controlled trial of factorial design *Br J Anaesth* 2002; **88**: 659–68

29 Pelkonen O, Maenpa J, Taavitsainen P, Rautio A, Raunio H Inhibition and induction of human cytochrome P450 (CYP) enzymes. *Xenobiotica* 1998; **28**· 1203–53

30 Wrighton SA, Stevens JC. The human hepatic cytochromes P450 involved in drug metabolism. *Crit Rev Toxicol* 1992, **22**. 1–21

31 Ulsamer B. Vecuronium bromide: modification of its pharmacodynamics by etomidate, cimetidine and ranitidine *Br J Anaesth* 1989; **37**: 504–9

32 *British National Formulary*. BMA Publications, 2002; **43**· 38

33 Honig PK, Woosley RL, Zamani K, Conner DP, Cantilena LR Changes in the pharmacokinetics and electrocardiographic pharmacodynamics of terfenadine with concomitant administration of erythromycin. *Clin Pharm Ther* 1992, **52**. 231–8

34 Ameer B, Weintraub RA. Drug interactions with grapefruit juice *Clin Pharm* 1997; **33**: 103–21

35 Walter-Sack I, Klotz U Influence of diet and nutritional status on drug metabolism. *Clin Pharm* 1996; **1**. 47–64

36 Merkel U., Sigusch H, Hoffman A. Grapefruit juice inhibits 7-hydroxylation of coumarin in healthy volunteers. *Eur J Clin Pharmacol* 1994; **46**: 175–7

37 Conney AH, Pantuck EJ, Hsiao KC, Kuntzman R, Alvares AP, Kappas A. Regulation of drug metabolism in man by environmental chemicals and diet. *Fed Proc* 1977, **36**: 1647–52

38 Koop DR. Oxidative and reductive metabolism by cytochrome P450 2E1. *FASEB J* 1992; **6**· 724–9

39 Batel P, Pessione F, Maitre C, Rueff B Relationship between alcohol and tobacco dependencies among alcoholics who smoke. *Addiction* 1995; **90**: 977–80

40 Blomqvist O, Ericson M, Johnson DH, Engel JA, Soderpalm B Voluntary ethanol intake in the rat: effects of nicotinic acetylcholine receptor blockade or subchronic nicotine treatment. *Eur J Pharmacol* 1996; **314**: 257–67

41 Horsmans Y. Major cytochrome P450 families. Implications in health and disease. *Acta Gastro-Enterelogica Belgica* 1997, **60**: 1–10

42 Inoue K, Yamazaki H, Shimada T. CYP2A6 genetic polymorphism and liver microsomal coumarin and nicotine oxidation activities in Japanese and Caucasians *Arch Toxicol* 2000; **73**· 532–9

43 Hayashi S, Watanabe J, Kawajiri KJ. Genetic polymorphism in the 5-flanking region change transcriptional regulation of the human cytochrome P4502E1 gene. *J Biochem* 1991, **110**: 559–65

44 O'Shea D, Davis SN, Kim RB, Wilkinson GR. Effect of fasting and obesity in humans on the 6-hydroxylation of chlorzoxazone: a putative probe of CYP2E1 activity. *Clin Pharmacol Ther* 1994; **56**: 359–67

45 Barash P, Cullen B, Stoelting RK. *Clinical Anaesthesia*, 2nd Edn. Lippincott, 1992; 1200

46 Gut J, Christen U, Huwyler J Mechanisms of halothane toxicity: novel insights. *Pharm Ther* 1993; **58**: 133–55

British Journal of Anaesthesia 89 (6)· 814–19 (2002)

BJA

CLINICAL INVESTIGATIONS

Phase behaviour of premixed 0.25% isoflurane in 50% nitrous oxide and 50% oxygen[†]

M. E. Tunstall and J. A. Ross*

Department of Environmental and Occupational Medicine, University of Aberdeen, University Medical School, Foresterhill, Aberdeen AB25 2ZD, UK

**Corresponding author. E-mail: j.a.ross@abdn.ac.uk*

Background. Isoflurane (0.25%) in premixed nitrous oxide and oxygen 50/50, v/v, (IN_2O), has been suggested for pain relief in labour.

Methods. Possible phase separation of this mixture was studied by analysis of samples from pre-filled cylinders as they were cooled.

Results. Condensation of isoflurane was found at 3.1°C in a cylinder, which held 8.7 MPa at 15°C. In a cylinder holding 13.8 MPa, which is the standard filling pressure stipulated by the National Health Service, the condensation temperature was –2.3°C. At the highest cylinder filling pressure investigated (14.15 MPa) the separation temperature was even less, –3.0°C. After exposure of cylinders to –40°C and complete phase separation of the mixture, complete mixing was achieved by 24 h storage in the horizontal position at room temperature and, either three complete inversions of the cylinder or mechanical rolling at 30 r.p.m.

Conclusions. These findings should assist the use and storage of IN_2O.

Br J Anaesth 2002; **89**: 814–19

Keywords: anaesthetics volatile, isoflurane; anaesthetic gases, nitrous oxide; anaesthetics, gases, premixed gases

Accepted for publication: July 18, 2002

The addition of 0.2–0.25% isoflurane to premixed nitrous oxide and oxygen, 50/50, v/v, is helpful for the relief of pain in labour.[1 2] Isoflurane and a 50% mixture of nitrous oxide in oxygen can be premixed together in the same storage cylinder at economical filling pressures and that such a mixture can be self-administered safely during labour[3] and for pain relief during the removal of chest drains.[4] Premixing anaesthetic agents with oxygen, stored under pressure in a single cylinder, allows a simple and safe method of administration but phase separation caused by cooling means that precautions are required for storage and handling. The characteristics of phase separation in a multi-component gas mixture are complex and alter with pressure. For example, if a cylinder of 50% nitrous oxide and oxygen (Entonox™), which is filled to 13.8 MPa at 20°C, is then cooled to –7°C, separation of nitrous oxide begins and a gas/liquid interface is formed. If the cylinder is partly emptied before cooling, for example to 11.7 MPa at 20°C, separation begins at the higher temperature of –5.5°C. Further emptying reduces separation temperature again.[5] This behaviour of individual gas mixtures is unpredictable. Experiments to determine phase separation at different temperatures and pressures are required.[6 7] We developed a technique of continuous sampling during externally applied cooling to measure separation of 0.25% isoflurane in equal parts of oxygen and nitrous oxide (IN_2O) and derived a partial phase envelope curve.

Methods

Phase separation experiments

A chrome molybdenum steel pressure cylinder of a nominal 10-litre water capacity (Faber, British Standard 5045), 535

[†] *Declaration of interest.* Patented by Aberdeen University. If commercial production were to occur, the university and the authors would benefit.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

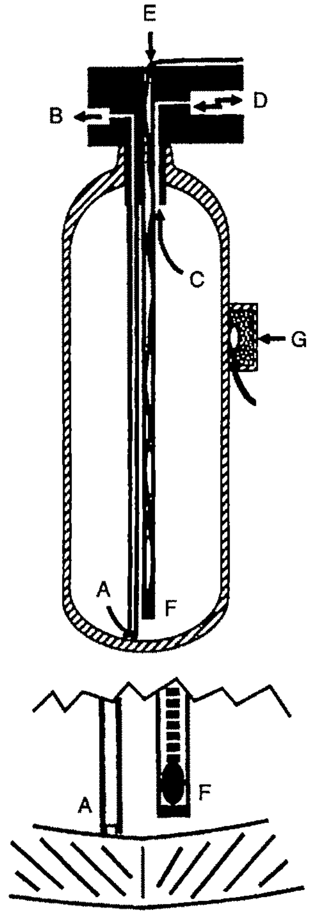


Fig 1 Variable scale broken diagram of test cylinder showing dip-tubes A and B, gas sample pathway from bottom of cylinder. C and D, gas sampling and filling pathway from the top of the cylinder. E and F, insertion pathway for thermistor probe into closed end dip-tube. G, shrouded thermistor probe on surface of cylinder.

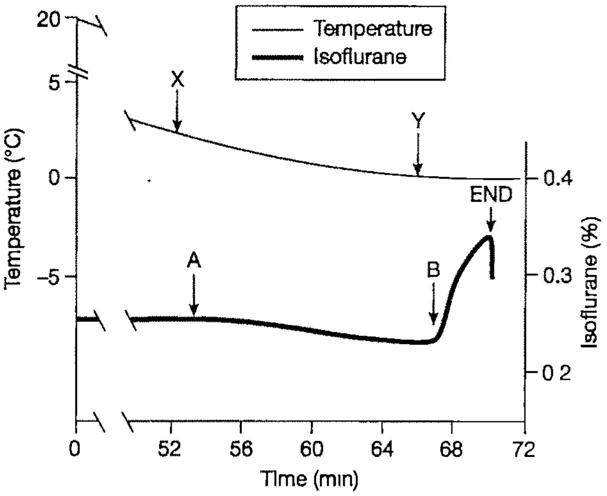


Fig 2 Trace of part of a recording of a cooling experiment. The upper trace is internal cylinder temperature and is offset to the left by the chart recorder pen position First dew formation is indicated by the decrease in isoflurane concentration at A. Heavy vapour formation is indicated by the increase in concentration at B, which is then stopped by closing the valve at END. The internal cylinder temperatures at which A and B occur are at X and Y, respectively, offset in position by the chart recorder. The weight of gas in the cylinder at point A was 1361 g.

mm long, was fitted with a brass head drilled through with four ducts. Dip tubes reaching within the cylinder were connected to three of the ducts, only two of which were used in this project (Fig. 1). With the cylinder standing upright, gas could be sampled through the ducts from two different levels within. Gas sampling from the top was via a duct opening directly from the head into the cylinder. Gas sampling from the bottom was through a 1.5-mm internal diameter dip tube with a notched tip touching the inner surface of the cylinder. Both ducts led to their own stop valves attached to the brass head, and then on to tapered needle metering valves (Nupro 'S' Series Fine Metering Valve with a 0.79 mm orifice). A 4.72 mm internal diameter dip tube with a blind end reached 6.5 mm clear of the cylinder bottom. It held a thermistor probe (Yellow Springs series 400) calibrated against a mercury thermometer (National Physical Laboratory) for measuring the gas temperature internally in the most dependent part of the cylinder.

The cylinder was attached to a gas filling manifold assembly and evacuated (Edwards Speedivac 2 vacuum pump). Forty-eight grams of isoflurane were weighed out (Sartorius 1773) at room temperature and injected into the cylinder from a glass syringe through a septum, which was then isolated from the filling system by a quarter-turn brass ball valve (Whitey). The cylinder was then set on a weighing scale (Sartorius IB 31000P) and filled with 3529 g of Entonox™ from a bank of cylinders to give a cylinder pressure of 14.35 MPa at 15°C. These quantities were calculated to give a final concentration of 0.25% isoflurane at standard atmospheric pressure and temperature.

Sampling tubes were attached to the cylinder head needle valves and a thermostatically controlled water circulator (Grant FH15) circulated warmed anti-freeze solution through plastic tubing coiled around the valves and attached tubing in order to prevent condensation of the test mixture after it had been sampled from the cylinder. After the warming coils were applied, the sampling arms were insulated with several layers of reflective plastic foil.

The test cylinder was cooled in a deep freeze chest (Derby), rated to operate at –40°C, within which an electric fan was used to circulate the air and a heat gun was used to slow cooling if it became too rapid. Three thermistor probes (Yellow Springs Instruments series 400) were calibrated against a mercury thermometer (National Physical Laboratory) and used for temperature recording. One was placed on the external surface of the cylinder half way along its length. It was shielded with a block of polystyrene foam

Table 1 Temperatures at which isoflurane dew and heavy vapour first formed during cooling, related to the amount of IN_2O gas in the cylinder at first dew formation

Weight of IN_2O gas in cylinder (g)	Temperature (°C)	
	At first dew	At heavy vapour
3499	–3.0	–3.4
3481	–3.0	–3.4
3466	–2.9	–3.4
3090	–0.6	–1.3
3027	–0.6	–1.3
2815	0.7	0.0
2620	1.5	0.3
2598	1.4	0.4
2358	2.4	1.0
2189	2.7	1.0
2143	2.8	0.9
1975	3.0	1.2
1830	3.0	1.1
1824	2.6	0.9
1738	2.9	0.9
1471	2.6	0.2
1361	2.4	0.0
1297	2.2	–0.9
1179	1.0	–1.8
1134	1.8	–2.5
1037	–0.4	–3.1
964	–0.4	–4.0
796	–2.4	–6.8
715	–3.1	–8.0

backed with a 9 cm diameter pad of closed cell 4-mm-thick neoprene foam. Two more temperature probes were placed within the freezer cabinet for observing the circulating air temperature both close to floor and at close to lid levels.

Three series of experiments were performed. Before each, the test cylinder was filled as described above and then lowered into the deep freeze. The lid was closed on top of the wires and tubes trailing over the edge, and continuous gas sampling was commenced in anticipation of the changes in isoflurane concentration. Gas flow from the sampling arms was checked at intervals and the metering valves were adjusted to allow a flow of approximately 1 g of IN_2O per minute using a specially marked flow meter. The gas sampled was analysed with an infra-red analyser (Datex Normac AA-102) for isoflurane and a paramagnetic analyser (Servomex type 570A/580A) for oxygen. Output signals from the analysers and thermistors were recorded on a flat bed recorder (Rikandenki RO3).

The temperature of the cylinder was allowed to decrease until a change in the concentration of isoflurane measured indicated the start of separation of the gas mixture. The first formation of isoflurane dew was taken to occur as soon as the concentration of isoflurane in the bottom sample began to decrease (Fig. 2). It was assumed that this was caused by isoflurane being lost as dew from the gas flow entering the dip tube becoming attached to immediately adjacent cold surfaces. The next stage is the formation of heavy vapour in the bottom part of the cylinder. As this happens, the concentration of isoflurane in the bottom sample increases and the concentration in the top sample decreases. The first formation of heavy vapour was noted when the decrease in isoflurane concentration stopped and a sustained increase had started (Fig. 2). The final stage is the formation of a pool of isoflurane liquid in the bottom of the cylinder. This contaminates the sampling system with large quantities of liquid isoflurane, which are then difficult to get rid of, so cooling was not allowed to progress to this stage. The valve on the sample path was closed and cooling stopped when the isoflurane concentration had increased to more than 0.3% and before liquid isoflurane had formed in the bottom of the cylinder.

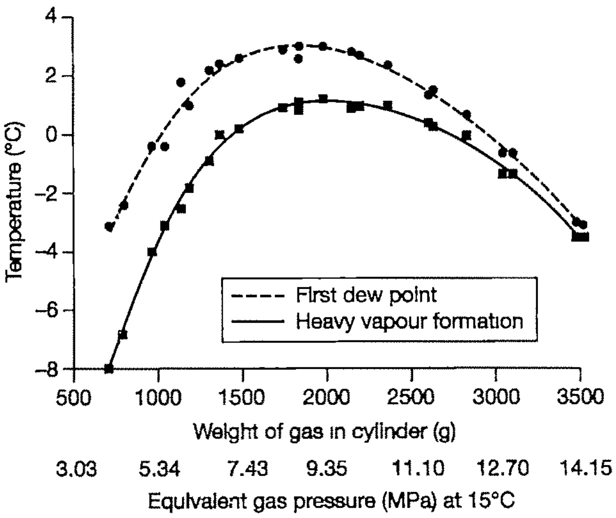


Fig 3 The effect of change in weight (filling pressure) of the contents of a cylinder of IN_2O on the temperatures at which dew formation begins and heavy vapour is formed.

After each experiment within a series, a measured quantity of gas was released to reduce the contents before the next experiment. The cylinder was then warmed, rolled at 30 r.p.m. for 30 min and allowed to stand overnight so that it would achieve a uniform temperature. The next morning the cylinder was weighed, its internal temperature and pressure recorded and another cooling study was done after a sample of the mixture had been analysed.

Remixing cylinder contents after their separation as a result of cooling

Two 12.2-litre capacity cylinders were used. They were filled with 54 g isoflurane and 4001 g Entonox™ to give a homogenous concentration of 0.25% isoflurane and then cooled to –40°C in a deep freeze chest for at least 24 h. This causes separation of isoflurane and nitrous oxide to form a pool of liquid in the dependent portion of the cylinder. The cylinders were then removed and stored either in the vertical or horizontal position for some time at room temperature before being checked. Mixing of cylinder contents was then

Table 2 Data from IN_2O (0.25% isoflurane and 51% oxygen) freezing and recovery experiments

Time sample measured	**Isoflurane** (%)	**Oxygen** (%)	**Cylinder position**	**Contents start/end** (g)	**Surface temperature** (°C)
Tested 25 h 43 min after removal from freezer. motionless recovery in horizontal position at ambient temperature					
16.54	0.27	50	Horizontal	3796/	18 7
17:00	0.11	55	Upright		18.6
17 05	0.39	47	Inverted		
17·11	0.16	54	Upright		
Cylinder rolled for 5 min at 30 revolutions min^{-1}					
17.43	0.25	51	Upright		
17.46	0 25	51	Inverted		
17·48	0.25	51	Upright	/3771	
Tested 29 h after removal from freezer. motionless recovery in upright position at ambient temperature					
15·59	0.01	79	Upright	3759/	17.5
16:03	0.015	77	Horizontal		12.5
16·08	0.52	27	Inverted		
Cylinder up-righted and then inverted three times					
16:15	0.18	58	Upright		13.0
16·19	0.30	46	Inverted	/3717	
Cylinder rolled for 10 min at 30 revolutions min^{-1}					
17 00	0 25	51	Upright	3717/	
17 04	0 25	51	Inverted	/3704	

Table 3 Data from IN_2O (0.25% isoflurane and 50% oxygen) freezing and recovery experiments. Oxygen was not measured in the first part of this experiment

Time sample measured	**Isoflurane** (%)	**Oxygen** (%)	**Cylinder position**	**Contents start/end** (g)	**Surface temp.** (°C)
Tested 24 h after removal from freezer: motionless recovery in horizontal position at ambient temperature					
14.56	0.23		Horizontal	3860/	
14:59	0.10		Upright		17.5
15·07	0.35		Inverted		
15:12	0 18		Upright		
Cylinder up-righted and then inverted three times					
15.17	0.25		Upright		
15:23	0.26		Inverted		
15.25	0 25		Upright	/3829	17.0
Tested 25 h after removal from freezer: motionless recovery in upright position at ambient temperature					
14:20	0.01	77	Upright	3829/	16 7
14:25	0.07	59	Horizontal		
Cylinder rolled for 5 min at 30 revolutions min^{-1}					
14:45	0.17	60	Upright		12 8
Cylinder rolled for 5 min at 30 revolutions min^{-1}					
15 00	0 24	51	Upright		13 7
15:04	0.26	49	Horizontal		
15:08	0.26	50	Inverted		
15:12	0.25	51	Upright		14.3
15:16	0.25	50	Inverted		
15.26	0 25	50	Upright	/3783	

attempted either by three complete inversions of the cylinder or by rolling the cylinder at 30 r.p.m. for 5 min. The contents of the cylinder were regarded as homogenous when the concentration delivered was unchanged by inverting the cylinder. Thermistor probes were attached to the cylinder surface at its mid-point in order to detect the temperature fall during inversion, which would be caused by the partial re-vaporization of agitated liquid contents. Gas analysis with the cylinder inverted was not carried out if there was free liquid in the cylinder. The cylinder contents were then mixed by either rolling at 30 r.p.m. or by repeated inversions. Each cylinder was used in each of the four test conditions.

Results

Phase separation experiments

The temperatures at which dew and then heavy vapour started to form during cooling, related to the weight of the IN_2O contained at the onset of dew formation, are shown in Table 1. Related to the weight of the gas mixture in the cylinder, they have a typical dome shape for the phase interfaces (Fig. 3). When the contents of the cylinder correspond to a filling pressure of 13.8 MPa absolute at 15°C (i.e. commercial filling pressure), the first formation of dew and then of heavy vapour occurred at –2.3 and –2.7°C, respectively. A further reduction in the cylinder contents gave a maximum temperature for first dew and for heavy vapour formation of at +3.1 and +1.3°C when contents were equivalent to filling pressures of 8.7 and 9.5 MPa, respectively (Fig. 3). The concentration of isoflurane in the test cylinder was measured as 0.25% both at the beginning and end of each series of experiments for each of the three cylinder fillings used.

Remixing cylinder contents after their separation because of cooling

There was detectable non-homogeneity of cylinder contents after both 24 and 48 h at room temperature in the horizontal position but no indication of the presence of a liquid phase. After the 24 h test, complete mixing was achieved either by rolling for 5 min at 30 r.p.m. (Table 2), or by three complete inversions of the cylinder (Table 3). After 24 h storage in the vertical position, a decrease in surface temperatures of the cylinders on the first inversion indicated the presence of liquid. The concentration of isoflurane was 0.52% and the concentration of oxygen was 27% in the sample taken on the first inversion. An even mixture was not achieved either by three complete inversions (Table 2) or by 5 min rolling (Table 3) but was restored after 10 min rolling (Tables 2 and 3).

Discussion

Condensation occurs in a gas when the saturated vapour pressure of the compound in question is exceeded. The saturated vapour pressure of nitrous oxide is 5.5 MPa at 20°C at atmospheric pressure[8] but in a mixture of 50% nitrous oxide in oxygen at 13.7 MPa the partial pressure of nitrous oxide is 6.85 MPa without condensation. Further, the mixture is stable down to −7°C. We have identified a similar increase in the saturated vapour pressure of isoflurane when mixed with 50% nitrous oxide in oxygen. The saturated vapour pressure of isoflurane at atmospheric pressure and 20.91°C is 33.41 kPa.[9] Yet at a pressure of 14.15 MPa a partial pressure of 35.38 kPa can exsist in the gaseous phase and the mixture is stable down to a temperature of −3.1°C.

Two effects explain this behaviour. The application of pressure to the condensed phase of a substance causes its vapour pressure to rise. This effect was first described by Poynting and is named after him.[10] In addition, gas phase molecules attract molecules out of the condensed phase by the process of gas solvation.[11] In high-pressure gaseous mixtures it is correct to think of the components as dissolved in each other. We studied the relative contribution of solvation and the Poynting effect in mixtures of isoflurane and 50% nitrous oxide in oxygen. At 10 MPa and 20°C the saturated vapour pressure of isoflurane was 95 kPa, an increase of 63 kPa from the saturated vapour pressure at atmospheric pressure.[6] The Poynting effect predicted an increase in vapour pressure of 22 kPa at this pressure and so an increase of 41 kPa could be attributed to gas solvation. The solvent property of a gas depends on its density, which increases with pressure and so higher cylinder pressures are associated with greater solvent power of the gas. However, the increase in solvent power of the gas phase may not be enough to prevent condensation if a fixed concentration is studied and at pressures up to 9.35 MPa 0.25% isoflurane becomes progressively less thermally stable. At higher pressures, however, there is a progressive improvement in stability indicating that the solvent capacity of the gas mixture increases.

Although the phase behaviour of multiple component gas mixtures can be estimated by modelling techniques we have found it easier and more direct to adopt an experimental approach.[6 7] This study has partially defined the phase diagram for the behaviour of 0.25% isoflurane in a mixture with equal parts of nitrous oxide and oxygen. A phase diagram is a map of the ranges of pressure and temperature at which each phase of a substance is the most stable (that is, has the lowest Gibbs energy).[11] The cricondentherm is the maximum temperature of a multi-component system at which liquid and vapour can exist in equilibrium, and above which liquid cannot be formed regardless of pressure. The cricondenbar is the maximum pressure at which liquid and vapour can co-exist.[12] At a temperature above its cricondentherm or at a pressure above its cricondenbar a mixture must be in a homogeneous phase.

We have defined the cricondentherm of IN_2O as 3.1°C. Importantly, we have shown that this occurs at a pressure typical of a cylinder that is between one-half and two-thirds full (assuming a usual cylinder pressure for medical gas of 13.8 MPa). The temperature at which separation will start to occur in a full cylinder is −2.3°C. In other words the contents of a full cylinder are more stable with respect to temperature than of one that is partially used. This has important implications for the transport, storage and use of IN_2O. An ambient outside temperature of −2.3°C is not unusual in the UK and so storage or transport in unheated areas would have to be avoided. An alternative approach might be to increase the cylinder filling pressure for the mixture, as this would make it more stable. Once the cylinder is in use, the thermal stability decreases until the cylinder pressure reaches 8.7 MPa. Further use improves stability again. Once a cylinder is in use it should be kept where ambient temperature cannot fall below 3.1°C. The freezing and recovery experiments show that the separated premixed gases are stable and that mechanical mixing after re-warming is necessary. It is better to store cylinders in the horizontal position.

References

1 Arora S, Tunstall M, Ross J. Self-administered mixture of Entonox and isoflurane in labour. *Int J Obst Anesth* 1992, **1**: 199–202

2 Wee MYK, Hasan MA, Thomas TA. Isoflurane in labour. *Anaesthesia* 1993; **48**: 369–72

3 Ross JAS, Tunstall ME, Campbell DM, Lemon JS. The use of 0.25% isoflurane premixed in 50% nitrous oxide and oxygen for pain relief in labour. *Anaesthesia* 1999; **54**: 1166–72

4 Bryden FMM, McFarlane H, Tunstall ME, Ross JAS. Isoflurane for removal of chest drains after cardiac surgery. *Anaesthesia* 1997; **52**: 173–5

5 Bracken AB, Broughton GB, Hill DW. Equilibria for mixtures of oxygen with nitrous oxide and carbon dioxide and their relevance to the storage of N_2O/O_2 cylinders for use in analgesia. *J Phys D Appl Phys* 1970; **3**: 1747–58

6 Uyanik A, Marr IL, Ross JAS, Tunstall ME. Preparation and high-pressure behaviour of pre-mixed volatile liquid anaesthetics in Entonox. *Br J Anaesth* 1994; **73**: 712P

7 Uyanik A. An investigation into the preparation, high-pressure behaviour and stability of premixed volatile liquid anaesthetics in Entonox. Aberdeen University Thesis, PhD, 1994

8 Grant WJ. *Medical Gases: Their Properties and Uses*, 1st Edn. Aylesbury, Buckinghamshire: HM+M Publishers, 1978

9 Nahrwold NL, Archer PG, Cohen PJ. Estimation of an equation relating saturated vapor pressure to temperature. *Anesthesiology* 1973; **39**: 444–6

10 Poynting JH. Change of state: solid-liquid. *Philosophical Magazine* 1881; **12**: 32–48

11 Atkins PW. Physical transformations of pure substances. In: Atkins PW, ed. *Physical Chemistry*, 5th Edn. Oxford: Oxford University Press, 1994; 183–91/240–53

12 Ahmed TH. Hydrocarbon phase behavior. In: Chilingar GV, ed. *Contributions in Petroleum Geology and Engineering*. Houston, Texas: Gulf Publishing Company, 1989; **7**· 1–35

British Journal of Anaesthesia 89 (6): 820–4 (2002)

Simulated use of premixed 0.25% isoflurane in 50% nitrous oxide and 50% oxygen[†]

J. A. Ross* and M. E. Tunstall

Department of Environmental and Occupational Medicine, University of Aberdeen, University Medical School, Foresterhill, Aberdeen AB25 2ZD, UK

**Corresponding author. E-mail: j.a.ross@abdn.ac.uk*

Background. Isoflurane (0.25%) in premixed nitrous oxide and oxygen, 50/50, v/v (IN_2O), has been suggested for pain relief in labour. Possible phase separation of the mixture was studied during simulated administration.

Methods. A sinusoidal pump set at stroke volume of 2 litres and a rate of 20–22 bpm and cycling for 1 min in three was used to simulate breathing during the painful contractions of labour.

Results. The temperature inside a 10-litre capacity cylinder did not drecrease sufficiently to cause separation of the gas mixture. Temperature in the demand valve decreased to −15.5°C and this caused a small amount of liquid formation within the valve. Accordingly, the inspired concentration during the first breath of mixture in a cycle could be transiently as high as 0.55%. The concentration observed at the patient connection after the first breath varied between 0.17 and 0.28%.

Conclusions. The system delivered a clinically acceptable performance although further development to avoid liquid condensation is needed.

Br J Anaesth 2002; **89**: 820–4

Keywords: anaesthetics volatile, isoflurane; anaesthetics gases, nitrous oxide; anaesthetics, gases, premixed gases

Accepted for publication: July 18, 2002

The addition of 0.2–0.25% isoflurane to premixed nitrous oxide and oxygen, 50/50, v/v (IN_2O), is helpful for the relief of pain in labour[1 2] and for the removal of chest drains.[3] Isoflurane and the proprietary preparation of 50% nitrous oxide in oxygen (Entonox™) can be premixed together in the same storage cylinder at economical filling pressures.[4] Premixed anaesthetic agents and oxygen, stored under pressure in a single cylinder, allows simple administration of a fixed dose of agent, but temperature reduction in the demand valve and in the cylinder during use may cause phase separation. Rapid removal of gas from a high-pressure cylinder causes cooling which can cause frosting of the cylinder and attached equipment. For IN_2O, if the temperature in a cylinder decreased below the separation temperature during use, it would become unsafe. Similarly, if the temperature of the delivery valve decreased below the separation temperature, then the volatile agent would condense and the characteristics of the mixture delivered might change. We studied how a full cylinder of IN_2O gas cools during simulated use and the concentration of isoflurane delivered.

Methods

Simulated use experiments

Isoflurane concentration and temperature in the administration set

A chrome molybdenum steel cylinder of nominal 12.2-litre water capacity rated to a working pressure of 20.7 MPa gauge (Faber, British Standard 5045) was used. The cylinder was filled with 4046 g (14.30 MPa at 15°C) of 0.24% isoflurane in a proprietary mixture of 50% nitrous oxide in oxygen (Entonox™, BOC Ltd) and fitted with a demand valve and administration set (Ohmeda). The patient connection of the breathing set was attached to the bag of a 5-litre 'bag in bottle' system with one-way valves attached to form as a patient simulator. The bottle was connected to a sinusoidal pump (P.K. Morgan Ltd. DEV2). The breathing

---

[†] *Declaration of interest.* Patented by the University of Aberdeen. If commercial production were to occur, the university and authors would benefit.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

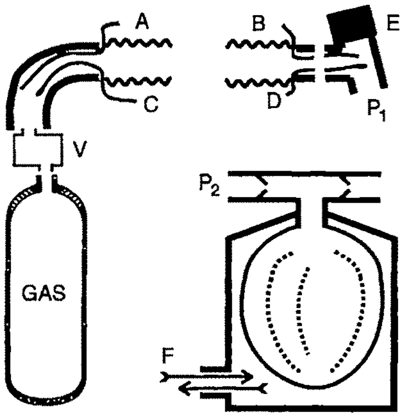


Fig 1 Variable scale broken diagram of breathing circuit and patient simulator. A and B, inserted gas sampling tubes; C and D, inserted thermistor probes within the Entonox™ breathing hose. V, position of demand regulator (Entonox™ valve) connecting gas cylinder to hose; P_1, patient end of breathing hose; P_2, connection point of patient end to 'bag-in-bottle' with uni-directional valves shown, E, closed off expiratory cap on Entonox™ hand-piece; F, connection to sinusoidal pump for actuating the 'bag-in-bottle' (patient simulator).

set used was of the standard type of corrugated black rubber fitted with an elbow connector (22 mm ID taper) at one end for connecting to a demand regulator, and an Entonox™ hand-piece (22 mm OD taper) at the other end. The hose was 1.5 m in length with an internal volume of approximately 750 ml (Fig. 1).

The volume of the IN_2O gas mixture pumped out of the exhalation port of the patient simulator was measured by a dry gas meter (Harvard) before being dumped through a passive scavenging system. The gas samples were analysed with an infra-red analyser (Datex Normac AA-102) for isoflurane and a paramagnetic analyser (Servomex type 570A/580A) for oxygen. Nitrous oxide concentration was calculated by the difference. Output signals from the analysers and thermistors were recorded on flat bed recorders (Rikandenki RO2 and RO3). Data points were taken from the recording paper. The recording pen was set at a gain of 25 mm per 0.1% isoflurane or per 5°C.

Gas was sampled for analysis at both ends of the breathing hose and temperature in the gas flow was measured by thermistors at the same points. A third thermistor probe was placed on the surface of the cylinder at its mid-point and was shrouded by a block of polystyrene covered in turn by a 5 cm diameter patch of 4 mm closed cell neoprene. A fourth probe recorded the room temperature at workbench level. All thermistor probes (Yellow Springs Instruments series 400) were calibrated against a mercury thermometer (National Physical Laboratory). Gas sampling was intermittently switched between the 'patient end' (hand-piece), and the 'valve end' (elbow connector). The sinusoidal pump was set to a tidal volume of 2 litres and a rate of 21 strokes min^{-1} and switched on for 1 min and off for 2 min by an automatic timer until the cylinder was empty. The experiment was conducted after the 12-litre cylinder had stood overnight and its external temperature was 20°C.

Internal cylinder temperature and isoflurane concentration

We used a 10-litre test cylinder, fitted with dip-tubes, as described previously.[4] It contained 3528 g (14.20 MPa at 15°C) IN_2O gas (containing 0.25% isoflurane). It was attached to the patient simulator via the Entonox™ demand regulator and breathing hose and emptied by the sinusoidal pump as described above for the 12.2-litre cylinder, but at 22 strokes min^{-1}. The cylinder and its appendages rested on electronic weighing scales (Sartorius IB 31000P) and the weight of the cylinder assembly and the volume of expired gas were recorded for each 3-min cycle. Internal and external cylinder temperatures were continuously recorded.

Three thermistor probes (Yellow Springs Instruments series 400) were calibrated against a mercury thermometer (National Physical Laboratory) and used for temperature recording. One was placed in a 4.72 mm internal diameter dip tube with a closed end that reached to 6.5 mm above the cylinder bottom. This measured the gas temperature internally in the most dependent part of the cylinder. Another was placed on the external surface of the cylinder half way along its length. It was shielded with a block of polystyrene foam backed with a 9 cm diameter pad of closed cell 4 mm-thick neoprene foam. The remaining sensor was used to measure room temperature.

Minimum temperatures, at the end of each cycle, were measured from the recording chart. The isoflurane concentration was continuously recorded alternately, from the distal (patient) end of the breathing hose and from inside the bottom of the cylinder via the long dip-tube.

Results

Isoflurane concentration and temperature in the administration set

Isoflurane concentration at the demand valve

The duration of the experiment was 201 min and measured pump output was 2797 litres. During the 1 min of breathing 'on' phase of the 3 min pump cycle, the temperature in the gas flow at the valve end of the hose decreased, the minimum temperature reached being −15°C (Fig. 2). The temperature at the patient end of the hose did not decrease below 15.3°C. Temperature changes at the patient end were minimal, the maximum change being 0.7°C. Values of the lowest temperature in each cycle are plotted (Fig. 2). The decrease of temperature in the demand valve caused condensation of isoflurane on cold surfaces so that during the 2 min 'breathing off' cycle, as the valve temperature increased, condensate evaporated causing an increase in concentration to a plateau level which did not exceed 0.55% and decreased during the experiment. This concentration decreased abruptly at the commencement of the first inspiration and was followed by a fluctuating pattern of

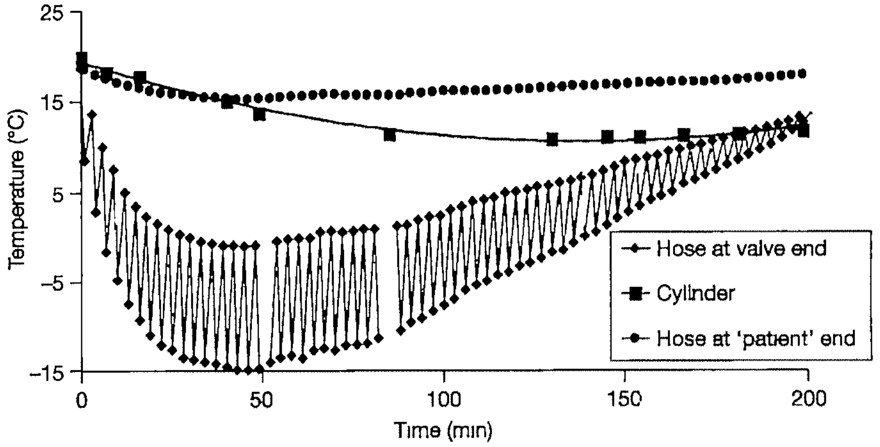


Fig 2 Temperature changes at the valve end of the breathing hose during the 'breathing on' cycle, and the temperature changes on the surface of the middle of the cylinder. Only the lower temperature of the minimal temperature swings at the patient end of the hose are plotted

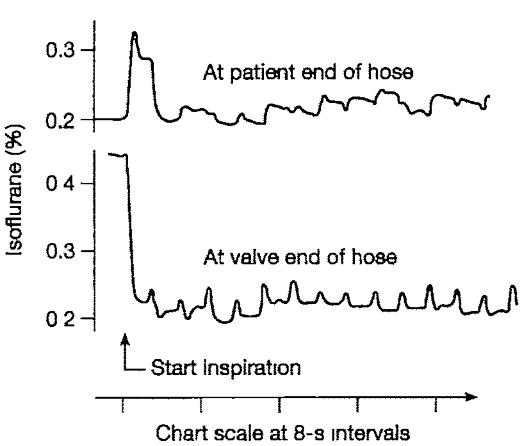


Fig 3 Isoflurane vapour concentrations at the valve and the patient ends of the breathing hose at the beginning of a 'breathing on' cycle (20 pump strokes at 2 litres stroke^{-1}).

isoflurane concentration during the 1 min 'breathing on' period (Fig. 3).

Isoflurane concentrations at the patient connection

During the 2 min 'breathing off' cycle, continuous gas sampling showed a slight and gradual decrease of isoflurane concentration. This increased sharply to a peak at the start of the first inspiration, which was followed by a fluctuating pattern of isoflurane concentration during the 1 min 'breathing on' cycle (Fig. 3). The peaks of isoflurane vapour concentration at first inspiration at the patient end of the hose did not exceed 0.4%. However, analysis was alternated between the patient and valve end of the hose and greater concentrations could have been present. The fluctuating pattern had a minimum of 0.17% recorded at 12 min and a maximum of 0.28% recorded at 57 min into the experiment. The variation in delivered concentration of isoflurane was greatest when the cylinder was full and virtually ceased when the temperature at the valve end of the breathing hose decreased to less than 3°C at the end of each 'breathing on' period. The contents of the cylinder showed no difference in the concentration of isoflurane in the cylinder between a sample taken at the beginning and one taken at the end of the experiment, indicating that no condensation of isoflurane had occurred in the 12.2-litre cylinder during the experiment.

Simulated use experiments: measurement of internal temperature and isoflurane concentration during cylinder emptying experiment

The experiment was conducted after the special 10-litre cylinder had stood overnight and its internal temperature was 16.2°C. During the experiment, room temperature rose from 16.1°C to a maximum of 18.9°C. At the end of the experiment when the pump was labouring to obtain gas through the system the pump was switched off. There was sufficient residual pressure within the cylinder to release 7 litres of gas containing 0.25% isoflurane, confirming that there had been no change in the concentration of isoflurane within the cylinder from beginning to end. Excluding the residual 7 litres, the total expired gas volume was 2460 litres for 56 cycles of 3 min each, equivalent to 43.93 litres for every minute the pump was on, representing constant emptying rate of 14.64 litres min^{-1}. The rate of cylinder emptying was linear as was the weight reduction of the cylinder contents, and was not affected by the marked frosting of the demand regulator, which occurred during the first half of the experiment. From the twelfth cycle onwards, the falling internal temperature curve from the experiment is shown with the dew curve[4] in Figure 4. It shows that the temperature fall during the experiment did not reach any point where phase separation could occur. This was confirmed by the consistency of the isoflurane sampling record throughout the experiment, both from the patient end

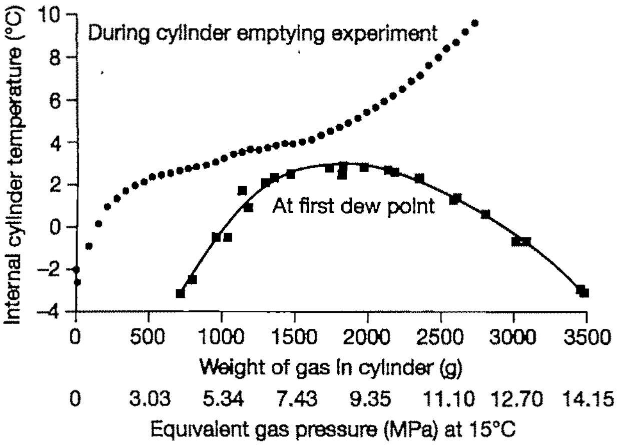


Fig 4 The cooling curve of the temperature (recorded internally at the bottom of the 10-litre cylinder), in the emptying experiment superimposed on the dew curve for IN$_2$O (the temperature in the cylinder at which isoflurane starts to condense)[4]

of the breathing hose and from the bottom of the cylinder via the long dip tube. The concentration of isoflurane was 0.25% in the cylinder gas both at the start and at the end of the experiment.

Discussion

We measured aspects of the performance of IN$_2$O delivery using a sinusoidal pump stroke volume of 2 litres. The rate was 22 strokes min^{-1} for the special 10-litre cylinder. The peak inspired flow to the pump was therefore 138 litres min^{-1}. An on–off cycle of 1 min on and 2 min off was chosen. The total volume of gas used was 2460 litres over a period of 168 min. These values were chosen to model the breathing pattern seen in the second stage of labour. Measurements have shown a peak inspiratory flow of 140.6 litres min^{-1}, tidal volume of 866 ml and a ventilatory frequency of 20 breaths min^{-1}, with contractions lasting 46 s with an interval between contractions of 2 min.[5] The mean consumption of a 50% nitrous oxide in oxygen mixture during labour in primiparous mothers was 764 litres with a maximum of 2580 litres. A representative period of time over which gaseous analgesia was used was the last hours of first stage and a second stage of 30 min.[5] Apart from peak inspiratory flow, therefore, the bench model exceeded mean values. In clinical use it would be unlikely that the model could be sustained for 168 min. If mean values for the use of 50% nitrous oxide are applied, the amount of gas used in the experiment would be typical of that used by three average primiparous mothers. In practice, therefore, the degree of cooling demonstrated during the bench experiments would be unusual.

We measured internal cylinder temperature during simulated use in order to see whether it would drop below the cricondentherm. (The cricondentherm is the maximum temperature of a multi-component system at which liquid and vapour can exist in equilibrium, and above which liquid cannot be formed regardless of pressure. The cricondenbar is the maximum pressure at which liquid and vapour can coexist.[6] At a temperature above its cricondentherm or at a pressure above its cricondenbar a mixture must be in a homogenous phase.) This did not happen and there was no separation of the isoflurane component of the gas mixture. Accordingly, we did not expect separation of the mixture during clinical use and residual gas analysis of cylinders returned from clinical use confirmed this.

The temperature decrease in the cylinder depends on a number of factors. Gas expansion in the cylinder causes an adiabatic decrease in temperature that is related to the reduction in pressure. Gas expansion through the demand valve causes local cooling and heat will be lost from the cylinder contents into the metal so cooled. On the other hand heat passes into the cylinder contents from the cylinder itself initially and then from the environment through the cylinder wall to offset these two factors. The cylinder used for this experiment was 10 litres nominal water capacity. Clearly the temperature changes in either larger or smaller cylinders will be different. In larger cylinders, the rate of pressure decrease will be less although the heat lost through a cooling demand valve will be the same. The heat available from the metal of the cylinder and through the cylinder wall will be greater because of its larger mass and surface area. As temperature decrease is related to pressure decrease this will be less in a larger cylinder. The converse is true for small cylinders and if breathing volumes are kept the same, the temperature in a small cylinder will decrease much more than in a large cylinder. Therefore, although our experiment indicates that condensation of isoflurane in a 10-litre cylinder is very unlikely, the same may not be true for smaller cylinders and further study would be needed if such cylinders were to be used clinically.

Saturated vapour pressure is temperature dependent and during the simulated use experiments the airflow temperature dropped to −15°C at the demand valve end of the administration circuit. During the use of the proprietary mixture Entonox™ the temperature of the demand valve may decrease to less than −20°C without affecting the function of the valve or the composition of the mixture delivered.[7] At −15°C the saturated vapour pressure of isoflurane is 3.5 kPa and that of nitrous oxide is 2112 kPa.[8] The pressure in the first stage of the demand valve is 1461 kPa and so the partial pressure of 0.25% isoflurane is 3.65 kPa and 50% nitrous oxide is 730.5 kPa. At temperatures of the order of −15°C and less, therefore, there is likely to be some condensation of isoflurane in the demand valve Also, because of the much higher pressure, there is certain to be small amounts of both liquid nitrous oxide and isoflurane in the part of the regulator before the first stage valve. This explains the varying concentration of isoflurane observed in the breathing circuit. During each stroke of the pump, the temperature in the demand valve is reduced. Once the saturated vapour pressure becomes less than the partial pressure of isoflurane in the mixture, some condensation occurs on the cold surfaces of the demand valve. During the 2 min rest phase, the demand valve temperature rises and, as the condensate vaporizes, the concentration of isoflurane in the gas sampled by the analyser rises. However, the maximum concentration seen as a result of this effect was 0.55% at the valve end. The peak concentration seen at the patient end of the hose was transient and affected the first breath of a cycle only.

After the transient peak at the start of a breathing period, the concentration at the patient end of the hose varied between 0.17 and 0.28% and this is comparable with the performance of an Oxford Miniature Vaporiser under similar circumstances.[1]

While the variation in delivered concentration identified here has caused no problem in the clinical use of IN_2O, the condensation of isoflurane that causes it is undesirable. Although the present system had an acceptable performance for clinical work, an administration system that prevents this effect would be desirable.

This agent, which has been suggested for use in pain relief in labour,[9] may be criticised for causing local atmospheric contamination. Although not the topic of this paper, the practical use of such agents should consider environmental control. The United Kingdom Control of Substances Harmful to Health Regulations (1999) place a statutory obligation on the users of anaesthetics to control the exposure of hospital staff within occupational exposure limits and lower if this is practicable. The addition of isoflurane to premixed 50% nitrous oxide in oxygen makes atmosphere control even more necessary than with the use of nitrous oxide alone as there is a requirement to consider the additive effects of such agent mixtures. We found it was possible to collect the expired gas from the expiratory valve of the breathing apparatus in a simple and convenient way using the wall suction equipment.[9] Other active scavenging systems would be as effective. In addition, our risk assessment of the use of the agent in a maternity suite did not reveal any problem before the clinical use of this agent.[10]

Acknowledgement

We would like to thank Dr Vivek Kulkarni for constructing the special electronic timing device for us in the Department of Bio-Medical Physics and Bio-Engineering, University of Aberdeen.

References

1 Arora S, Tunstall M, Ross J. Self-administered mixture of Entonox and isoflurane in labour. *Int J Obst Anesth* 1992; **1**: 199–202
2 Wee MYK, Hasan MA, Thomas TA. Isoflurane in labour. *Anaesthesia* 1993; **48**: 369–372
3 Bryden FMM, McFarlane H, Tunstall ME, Ross JAS. Isoflurane for removal of chest drains after cardiac surgery. *Anaesthesia* 1997; **52**: 173–5
4 Tunstall ME, Ross JA. Phase behaviour of premixed 0.25% isoflurane in 50% nitrous oxide and 50% oxygen. *Br J Anaesth* 2002; **89**: 814–19
5 Crawford JS, Tunstall ME. Notes on respiratory performance during labour. *Br J Anaesth* 1968; **40**: 612–4
6 Ahmed TH. Hydrocarbon phase behavior. In: Chilingar GV, ed. *Contributions in Petroleum Geology and Engineering*. Houston, Texas: Gulf Publishing Company, 1989; **7**: 1–35
7 Hill DW. Pressure gauges and regulators. In: Hill DW, ed. *Physics Applied to Anaesthesia*. London: Butterworths, 1972; 47–69
8 Rodgers RC, Hill GE. Equations for vapour pressure versus temperature: derivation and use of the Antoine equation on a hand-held programmable calculator. *Br J Anaesth* 1978; **50**: 415–24
9 Ross JAS, Tunstall ME, Campbell DM, Lemon JS. The use of 0.25% isoflurane premixed in 50% nitrous oxide and oxygen for pain relief in labour. *Anaesthesia* 1999; **54**: 1166–72
10 Ross JAS. Isoflurane Entonox mixtures for pain relief during labour. *Anaesthesia* 2000; **55**: 711–2

British Journal of Anaesthesia **89** (6). 825–31 (2002)

Equipment problems during anaesthesia—are they a quality problem?

S. Fasting* and S. E. Gisvold

Department of Anaesthesia and Intensive Care, University Hospital of Trondheim, N-7006 Trondheim, Norway

**Corresponding author. E-mail: sigurd.fasting@medisin.ntnu.no*

Background. Anaesthesia equipment problems may contribute to anaesthetic morbidity and mortality. The magnitude and pattern of these problems are not established. We wanted to analyse the frequency, type and severity of equipment-related problems in our department, and if additional efforts to improve safety were needed.

Methods. The study is based on a system in which anaesthesia-related data are recorded from all anaesthetic cases on a routine basis. The data include intraoperative problems and their severity. When a problem occurs, the anaesthetist responsible for the case writes a short description of the event on the anaesthetic chart. From all recorded cases of general and regional anaesthesia, we selected cases recorded with anaesthetic 'equipment/technical problems'. These charts were retrieved from departmental archives for analysis.

Results. From 83 154 anaesthetics, we found the frequency of anaesthetic equipment problems to be 0.05% during regional anaesthesia, and 0.23% during general anaesthesia. One-third of problems involved the anaesthesia machine, and in a quarter, human error was involved. No patient died and none suffered any lasting morbidity.

Conclusion. The rate of equipment problems was low, and most often of low severity. Aside from improvements in routines for preoperative equipment checks, no specific strategies for problem reduction could be suggested. The incidence of equipment problems is not a good quality indicator because of the low rate of occurrence. However, recorded equipment problems may be useful for improving quality, by analysing causative factors, and suggesting preventative strategies.

Br J Anaesth 2002; **89**: 825–31

Keywords: anaesthesia; complications, equipment problems; quality improvement

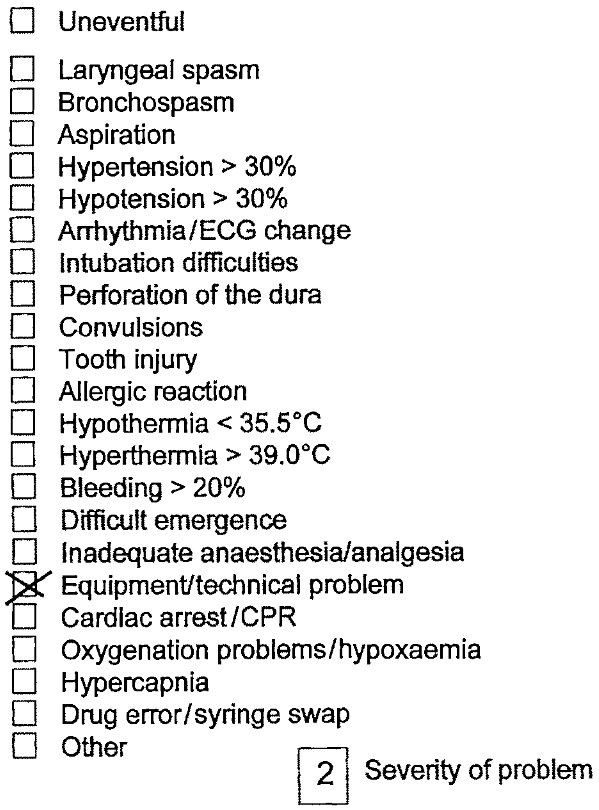
Accepted for publication: July 30, 2002

Anaesthesia equipment is important for the safe conduct of anaesthesia, but equipment malfunction may also contribute to morbidity and mortality.[1–3] The anaesthesia machine has most often been involved in equipment-related morbidity,[1 4–7] and this has led to extensive use of preoperative checklists. Previous studies have shown that the frequency of equipment problems has varied from 0.2 to 2.1%. However, study design, method of problem reporting, and problem classification have varied. In addition, routines for the preoperative checking of anaesthesia machines and other equipment have not been specified.[4 5 8–11] In 1985, our department instituted a system for the recording of anaesthetic-related data.[12] We have studied equipment problems recorded from 83 154 consecutive cases from 1996 to 2000. The primary aim of our study was to analyse the frequency, type, and severity of equipment-related problems in relation to our current procedures for the checking of equipment and current working routines. We questioned whether additional efforts were needed to improve safety with respect to equipment issues. A secondary aim was to illustrate how a routine-based system for problem recording can simplify this type of continuous quality improvement in a department.

Methods

The study is based on departmental data recorded over a 5-yr period (1996–2000) from 83 154 consecutive anaesthetics. One part of our standard anaesthetic record is devoted to specified data fields that must be completed by

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002



☐ Uneventful

☐ Laryngeal spasm
☐ Bronchospasm
☐ Aspiration
☐ Hypertension > 30%
☐ Hypotension > 30%
☐ Arrhythmia/ECG change
☐ Intubation difficulties
☐ Perforation of the dura
☐ Convulsions
☐ Tooth injury
☐ Allergic reaction
☐ Hypothermia < 35.5°C
☐ Hyperthermia > 39.0°C
☐ Bleeding > 20%
☐ Difficult emergence
☐ Inadequate anaesthesia/analgesia
☒ Equipment/technical problem
☐ Cardiac arrest/CPR
☐ Oxygenation problems/hypoxaemia
☐ Hypercapnia
☐ Drug error/syringe swap
☐ Other

2 Severity of problem

Fig 1 When a problem occurs, the anaesthetist writes a short description of the problem on the anaesthetic chart, and marks the problem check-box according to problem type and severity.

the end of the case. The data fields on all anaesthesia charts are checked for completeness and accuracy by a consultant anaesthetist (SF or SEG) before secretaries enter data into the database. A copy of the anaesthetic record is stored in the department.

One of the data fields is a check-box for 'intraoperative problems' (Fig. 1), including a list of 22 common anaesthetic problems, and a field for the severity. One of the problems is 'equipment/technical problems'. The anaesthetist responsible for the patient writes a short description of the event and marks the check-box accordingly. If the case was 'uneventful', this also must be indicated. Other data fields relate to the patient, the operation, type of anaesthetic, and timing of events.

An 'intraoperative problem' is defined as 'an event that requires one or more measures, either to prevent further complications, or to treat a situation that is currently or potentially serious, and does not routinely occur during the conduct of anaesthesia'. The problem is graded according to severity. Severity 'Grade 1' is a trivial problem, 'Grade 2' is a moderately difficult problem, with some effect on the patient, but of a low severity. 'Grade 3' is a serious situation that either proves very difficult to handle or causes a serious deterioration in the patient's state, which may or may not contribute to postoperative morbidity. 'Grade 4' problems are associated with a fatal outcome.

About 16 500 anaesthetics are given in our hospital each year, and most types of surgery are performed (Trondheim University Hospital, 960 beds, annual admission rate 43 000 patients, in 1999). In Norway, as in the rest of Scandinavia, the physician anaesthetist works in cooperation with a qualified nurse anaesthetist who has 18 months postgraduate education in anaesthesia. The doctor has the medical responsibility. Each morning the nurses do an extensive check of the anaesthesia machine according to departmental procedures. This check includes medical gas supplies, flowmeters, oxygen failure protection, vaporizers, machine/breathing system leakage, machine/breathing system function, ventilator, scavenging, suction and intubation equipment. Between patients a simpler check is performed. One nurse is working full-time to educate all staff on equipment issues, and the department engages two engineers for continuous maintenance and repair of equipment.

The charts recorded with anaesthetic 'equipment/technical problem' were retrieved from our departmental archives. They were sorted according to the type of equipment involved and analysed by the authors according to frequency, severity and contributory factors. We analysed not only cases of 'true equipment failure' where the equipment failed to perform as specified, but also equipment problems where 'human error', 'failure to check', or some form of failing 'human–equipment' interface was the most important factor. We did not include problems with surgical equipment or 'technical' problems with anaesthetic or surgical procedures.

For categorical data, we used a χ^2-test or Fisher's exact test as appropriate. We used a 'χ^2-test for trend' for testing trends in binomial proportions.[13] $P<0.05$ was considered statistically significant.

Results

We recorded 83 154 anaesthetics during 1996 to 2000. The age and ASA-class of the patient and type of surgery are presented in Table 1.

Frequency of equipment problems (Table 2)

We retrieved 198 charts in which 'equipment/technical problems' were recorded. Of these, 41 were not included in the final analysis, as 29 cases represented difficulties with the actual performance of anaesthetic or surgical procedures, six records were entered incorrectly into the database, two charts were missing from the archives, and in four cases the contributory factors of the problems were not described. We reviewed the resulting 157 cases of anaesthetic equipment problems (0.19% of all cases). These equipment problems represented 1.1% of all recorded problems (157/13 756). The occurrence of equipment problems was higher during general anaesthesia than regional anaesthesia (0.23% *vs* 0.05%), in contrast to other (non-equipment related) problems, where the frequency was

Table 1 Patient characteristics—83 154 anaesthetics

	Regional anaesthetics		General anaesthetics		All anaesthetics	
	n	%	*n*	%	*n*	%
Age 0–20 yr	308	1.5	17 357	27.7	17 665	21.2
Age 20–60 yr	9598	46.7	31 974	51.1	41 572	50.0
Age >60 yr	10 658	51.8	13 259	21.2	23 917	28.8
ASA I	5401	26.3	21 079	33.7	26 480	31.8
ASA II	9128	44.4	27 718	44.3	36 846	44.3
ASA III	5197	25.3	9646	15.4	14 843	17.9
ASA IV	826	4.0	3923	6.3	4749	5.7
ASA V	12	0.1	224	0.4	236	0.3
General surgery	4804	23.4	18 130	29.0	22 934	27.6
Orthopaedic surgery	13 122	63.8	13 319	21.3	26 441	31.8
Neurosurgery	18	0.1	3881	6.2	3899	4.7
Gyn/Obst surgery	1956	9.5	13 256	21.2	15 212	18.3
Other	664	3.2	14 004	22.4	14 668	17.6
All anaesthetics	20 564	100.0	62 590	100.0	83 154	100.0

Table 2 Frequency and severity of problems Higher frequency of equipment problems during general anaesthesia compared with regional anaesthesia, but increased frequency of 'other problems' during regional anaesthesia (*$P<0.01$)

	Regional anaesthetics		General anaesthetics		All anaesthetics	
	n	%	*n*	%	*n*	%
Equipment problems						
Severity Grade 1–2	10		143		153	
Severity Grade 3	0		4		4	
Severity Grade 4	0		0		0	
Total	10	(0.05)*	147	(0.23)*	157	(0.19)
Other problems						
Severity Grade 1–2	3492	(17.0)	9671	(15.4)	13 163	(15.8)
Severity Grade 3	39	(0.2)	343	(0.5)	382	(0.5)
Severity Grade 4	0		54	(0.1)	54	(0.1)
Total	3531	(17.2)*	10 068	(16.1)*	13 599	(16.4)
All problems	3541	(17.2)	10 215	(16.3)	13 756	(16.5)
All cases	20 564		62 590		83 154	

slightly higher during regional anaesthesia (17.2% *vs* 16.1%).

Severity of equipment problems

As presented in Table 3, most equipment problems (n=112) were trivial (Severity Grade 1). About one-quarter (n=41) were of intermediate severity (Severity Grade 2), and four were serious (Severity Grade 3). All the serious problems and 29 of the intermediate problems affected the patient to some degree (Table 4), but no patient suffered any lasting morbidity or needed prolonged postoperative care.

In four cases, the problems were judged as serious (Severity Grade 3). In one case the ventilator was inadvertently turned off during anaesthesia. This was a new anaesthetic machine, where the 'power button' protruded from the cabinet, and it was inadvertently pushed by the anaesthetist. The ventilator stopped and the patient's pulse oximeter reading decreased to 45% before the error was detected. In one case, the non-invasive arterial pressure readings were falsely high, and the patient received a large dose of volatile anaesthetic, while the patient in reality was severely hypotensive. In two cases the cardiopulmonary bypass machine was involved: in one there were misconnection and oxygenation problems; in the other case the system was primed incorrectly. All these problems involved elements of human error.

Types of equipment involved (Table 3)

One-third of the problems (49/157) occurred with the anaesthesia machine, with the most common problem being leakage from, and misconnection of, the breathing system (n=24). Other problems included gas leakage from the vaporizer–machine connection (n=7), leakage in the ventilator (n=8), and malfunction of the one-way valve.

The majority of other problems occurred with invasive and non-invasive arterial blood pressure monitoring

Table 3 Type of equipment involved and severity of problem

Equipment involved	Severity Grade 1 *n*	Severity Grade 2 *n*	Severity Grade 3 *n*	Total equipment problems *n*
Anaesthesia machine	26	22	1	49
Invasive arterial pressure	14	4		18
Non-invasive arterial pressure	14	1	1	16
Gas analyser	12			12
Other monitor	8	2		10
ECG	10			10
Cardiopulmonary bypass machine		5	2	7
Pulse oximeter	7			7
Endotracheal tube	4	1		5
Infusion pump	4	1		5
Temperature measurement	4			4
Capnograph	3	1		4
I.V. access	1	1		2
Central venous pressure	2			2
Defibrillator	1	1		2
Blood warmer	1			1
Chest drain		1		1
Laryngoscope	1			1
Urometer		1		1
Total	112	41	4	157

Table 4 Untoward effects on the patient caused by equipment problems

Equipment involved	Problem	Effect on patient	*n*
Anaesthesia machine	Misconnection	Hypoxaemia	5
	Ventilation problems	Hypoxaemia	2
	Low flow in Mapleson-D system	Hypercapnia	2
	Valve occlusion	High airway pressure	1
	Power supply—ventilator stopped	Hypoxaemia	1
	Adult equipment to child	Hypercapnia	1
	Vaporizer failure	Hypotension	1
Cardiopulmonary bypass machine	Short stops from various causes	Hypoperfusion, short periods	7
Non-invasive arterial pressure	Error in measurement	Undetected hypotension	4
Invasive arterial pressure	False low pressures	Unnecessary pressor treatment	3
Infusion pump	Malfunction	Drug overdose, hypotension	2
Urometer	Occlusion in set	Unnecessary fluids and diuretics	1
Defibrillator	Failure to shock	Delayed treatment	1
I.V. access	Disconnection	Hypovolaemia, hypotension	1
Chest drain	Disconnection	Lung collapse	1
Total			33

equipment, and other monitoring equipment. Most of the problems with invasive arterial blood pressure equipment represented low readings from a radial artery cannula compared to the aortic cannula during cardiac surgery. However, measurement errors, drifting, and cable failure also occurred. Non-invasive arterial blood pressure equipment failure was also common, and related to technical failure—including leaks from the tubing and cuff. Other problems related to malfunction of other monitors, and malfunction of the cardiopulmonary bypass machine during cardiac surgery.

Human error

About one-quarter of the equipment problems (n=40) were considered to be related to human error on the part of the users (Table 5). Twenty-nine of the problems concerned the anaesthesia machine, and of these, 18 were related to inadequate pre-use checks. Most of these errors occurred when the anaesthesia machine was checked between cases, rather than at the start of the day. Contributing factors were 'last-minute changes' because of a change in schedule (change in type of breathing system, ventilator, or type of anaesthesia).

Continuous quality improvement

No trends were noted in the rate of occurrence of equipment problems between 1996 and 2000. In the same period, we recorded an increased occurrence of other problems (Table 6).

Table 5 Human errors contributing to equipment problems

Equipment involved	Problem	*n*
Anaesthesia machine	Misconnected patient systems	13
	Undetected leakage from patient systems	5
	Wrong gas flow—patient system	2
	Power accidentally turned off	1
	Vaporizer leakage—after changeover	6
	Other	2
Non-invasive arterial pressure	False normal readings, delayed detection of low arterial pressure	3
Invasive arterial pressure	False low readings—treated with vasopressor	3
Cardiopulmonary bypass machine	Misconnection and wrong priming of system	2
Endotracheal tube	Kinked tube, not checked, bronchodilators given	1
Laryngoscope	Low batteries, no spare immediately available	1
Chest drainage	Disconnection—wrong connectors used	1
Total		40

Table 6 Variation in occurrence of problems from 1996 to 2000 There was no change in frequency of equipment problems, but an increase in frequency of other problems

	1996	1997	1998	1999	2000	Trend	*P*-value
Equipment problems	45	25	29	25	33	No change	0.25
Other problems	2644 (15.5%)	2730 (16.0%)	2726 (16.5%)	2645 (17.3%)	2854 (17.1%)	Increase	<0.001
Cases per year	17 023	17 020	16 544	15 829	16 738		

Discussion

Having prospectively recorded problems in 83 154 cases of anaesthesia, we found equipment problems to be rare, and of low severity. Human errors (for example failure to check equipment and man–machine interaction failure) were important factors, in addition to 'pure' equipment failure. The low frequency of equipment problems limits its usefulness as a numerical quality indicator. However, analysis of patterns and causes of these problems can be a useful part of a quality assurance programme in a department.

Methodology

In all incident reporting, under-reporting is a potential problem. This is related to the added workload from completion of forms, a belief that reporting is of limited value, and fear of consequences of reporting.[14–17] We believe that the reporting compliance in our study is good. All patients receiving an anaesthetic were followed, and included in the study. The incidents were recorded in a prospective manner, and as information from all cases was included, important events were less likely to be missed. This is in contrast to studies where information is collected only from selected samples of patients.

Our system is designed to add minimal workload, as all recording is done directly on the anaesthetic chart, and no additional form is needed. We are using the data actively in the department, for problem discussions and quality projects, and we have created a non-punitive attitude towards the occurrence of problems.[12] All cases are recorded, the recording is obligatory, and both a physician and a nurse are involved in every case. The recording has been part of departmental routine for 15 yr, and definitions and severity assessment are continuously discussed in departmental meetings. Consequently, we believe that the agreement between observers is good. We also believe that the total frequency of problems and the frequency of equipment problems are representative of the occurrence of these problems in our practice, and are a result of routines for checking and maintenance of equipment in the department, and routines for follow-up when problems occur.

Frequency and severity of equipment problems

Four studies have been published representing mandatory reporting, with data recorded from all anaesthetic cases.[8–11] Our results are of the same magnitude as those of Cohen and colleagues[8] who found an incidence of 0.1–0.4% for equipment problems in 27 184 cases of anaesthesia from four different hospitals. In that study, a check-off form was completed for every patient, and 18 types of intraoperative problems were included in the data set. However, severity was not assessed. The frequency of total problems varied from 14.9% to 27.8% amongst the four hospitals.

Three studies have been published from a large German quality assurance project concerning perioperative incidents (both operating room and recovery room).[9–11] Data were collected from all anaesthetics, 63 types of incidents and five levels of severity were defined. The frequency of equipment problems was 0.7% in 18 350 cases,[9] 0.9% in 26 907 cases,[10] and 1.2% in 96 000 cases.[11] The frequency of all problems was 23.2%, 27.9% and 22% respectively.[9–11] We found a lower occurrence of total equipment problems and total problems than in the German studies. The cause of this is difficult to discern, as the German studies included the whole perioperative period and the intraoperative problems are not reported separately. In addition, definitions and classifications were different. Finally, there is of course a possibility of differences in problem occurrence, reporting compliance, or both. However, the general conclusions from these and our studies are similar, as equipment problems were rare and of low severity, but some had untoward effects on patients, without causing any lasting morbidity. These problems do carry a potential for serious adverse outcome, and preventative measures are important.[1 3 7 9 18]

Other studies have collected data by voluntary reporting only of problem cases. The overall problem figures are generally lower, as under-reporting is well recognized.[16 17] Short and colleagues[5] reported a frequency of 0.23% of equipment/breathing system problems in 16 379 anaesthetics, but an overall problem rate of only 0.76%. Spittal and colleagues[4] reported a 2% incidence of equipment-related problems in 5056 cases, with an overall problem rate of 6.68%. The case mix, routines for preoperative checking of the anaesthesia machine, and level of maintenance of other equipment, were not specified in these studies.

Type of equipment involved

The anaesthesia machine, including the breathing system, was the most common cause (31%) of equipment problems in our study. This was also the most common cause in the studies by Bothner, Georgieff and Schwilk (30%),[11] and Schwilk and colleagues (22%).[10] Also, in other incident studies where the denominator is not known,[1 4–6] problems related to the anaesthesia machine were most common, ranging from 52 to 73%.

We found most of the anaesthesia machine problems to be related to the breathing system, as has been found in other studies where this information is supplied.[1 4–6] The breathing system is often reconnected for cleaning and change of system between patients, and this may predispose it to errors, despite the routines for checking the machine at the start of the day.

Non-invasive and invasive arterial pressure measurements were involved in many of the equipment problems. This equipment has many potential problems, and readings may not be correct. This predisposes it to errors, and our findings are a reminder that numbers from invasive and non-invasive automated arterial blood pressure measurement should be constantly evaluated against the patient's clinical condition.

Human error

Human error and misuse of equipment have been shown to be more common than 'true' equipment failure.[3 5] In our study, human error was the main contributing factor in one-quarter of cases, and most of these involved the anaesthesia machine. The main cause was insufficient checking of the anaesthesia machine before use, especially between cases. This was also shown by Short and colleagues.[19] The problems often occurred as a consequence of 'last-minute modifications', when breathing systems and vaporizers were changed after the checking procedure had been performed.

To reduce the possibility of human error causing equipment problems a three-level approach has been suggested: (i) when possible, equipment should be designed such that the possibility of human error is minimized; (ii) if human error cannot be prevented, systems should be designed to minimize the injury caused by such errors; (iii) if neither of the previous safety approaches is possible, the system should be equipped with monitors and alarms to alert the user of an adverse condition that may be caused by equipment failure or change in the patient's condition. This approach is an example of a 'systems' approach to error management, where the working environment of the anaesthetist is optimized to avoid errors.[20 21]

Continuous quality improvement

We found no change in occurrence of equipment problems during the period of our study, while there was an increasing trend for other problems. However, the low rate of equipment problems limits statistical appraisal, as variation may be the result of chance. The low rate of equipment problems also limits its use as a continuous quality indicator, as changes in occurrence caused by efforts to improve are difficult to separate from natural variation. Therefore, the most suitable analysis of these data may be as 'sentinel events', where problems are analysed individually, or in groups, to elucidate causative factors and preventative measures, rather than a numerical approach.

The low rate of equipment problems recorded indicates that our routines for use, checking and maintenance of equipment are adequate. However, there is still a potential for serious problems, and strategies to prevent human error should be implemented as this contributed to a quarter of problems. In addition, an improved check between cases may reduce the occurrence of equipment problems with the anaesthesia machine, which was the main cause of problems.

Ideally, follow-up of problems as part of continuous quality improvement efforts should lead to a decreased problem frequency. Short and colleagues[19] studied improvements in anaesthetic care resulting from a critical incident reporting programme, but found no change in incidence of problems. However, the programme was considered effective in detecting latent system errors. Changes in the frequency of problems may be explained as a result of quality-related activities in the department, but also changes in reporting compliance, or changing anaesthesia practice may influence the results. A routine-based recording system will give us the possibility of evaluating problem rates, as the total number of anaesthetics is known, but care must be taken when the occurrence is rare.

Conclusion

With our checking and maintenance routines, we found equipment to cause few problems, both related to number of cases (0.19%), and related to the occurrence of other problems during anaesthesia (1.1%). Human factors were important causes of problems, and the anaesthesia machine was most often involved. Although we recorded no morbidity from equipment problems in 83 154 cases, both this and other studies have indicated that a potential for equipment-related morbidity exists. The type of data retrieved from our analysis provides valuable information for departmental quality projects.

Acknowledgements

The study is supported with grants from the Norwegian Medical Research Council.

References

1 Cooper JB, Newbower RS, Kitz RJ. An analysis of major errors and equipment failures in anesthesia management: considerations for prevention and detection. *Anesthesiology* 1984; **60**: 34–42

2 Gilron I. Anaesthesia equipment safety in Canada: the role of government regulation. *Can J Anaesth* 1993; **40**: 987–92

3 Caplan RA, Vistica MF, Posner KL, Cheney FW. Adverse anesthetic outcomes arising from gas delivery equipment: a closed claims analysis. *Anesthesiology* 1997; **87**: 741–8

4 Spittal MJ, Findlay GP, Spencer I. A prospective analysis of critical incidents attributable to anaesthesia. *Int J Qual Health Care* 1995; **7**: 363–71

5 Short TG, O'Regan A, Lew J, Oh TE. Critical incident reporting in an anaesthetic department quality assurance programme. *Anaesthesia* 1993; **48**: 3–7

6 Webb RK, Russell WJ, Klepper I, Runciman WB. The Australian Incident Monitoring Study. Equipment failure: an analysis of 2000 incident reports. *Anaesth Intens Care* 1993; **21**: 673–7

7 Bothner U, Georgieff M, Schwilk B. The impact of minor perioperative anesthesia-related incidents, events, and complications on post-anesthesia care unit utilization. *Anesth Analg* 1999; **89**: 506–13

8 Cohen MM, Duncan PG, Pope WD, *et al.* The Canadian four-centre study of anaesthetic outcomes: II. Can outcomes be used to assess the quality of anaesthesia care? *Can J Anaesth* 1992; **39**: 430–9

9 Schwilk B, Muche R, Bothner U, Goertz A, Friesdorf W, Georgieff M. Quality control in anesthesiology. Results of a prospective study following the recommendations of the German Society of Anesthesiology and Intensive Care. *Anaesthesist* 1995; **44**: 242–9

10 Schwilk B, Muche R, Treiber H, Brinkmann A, Georgieff M, Bothner U. A cross-validated multifactorial index of perioperative risks in adults undergoing anaesthesia for non-cardiac surgery. Analysis of perioperative events in 26 907 anaesthetic procedures. *J Clin Monit Comput* 1998; **14**: 283–94

11 Bothner U, Georgieff M, Schwilk B. Building a large-scale perioperative anaesthesia outcome-tracking database: methodology, implementation, and experiences from one provider within the German quality project. *Br J Anaesth* 2000; **85**: 271–80

12 Fasting S, Gisvold SE. Data recording of problems during anaesthesia: presentation of a well-functioning and simple system. *Acta Anaesthesiol Scand* 1996; **40**: 1173–83

13 Rosner B. Chi-square test for trend in binomial proportions. In: *Fundamentals of Biostatistics*. Pacific Grove, CA: Duxbury Press, 2000; 397–400

14 Sanborn KV, Castro J, Kuroda M, Thys DM Detection of intraoperative incidents by electronic scanning of computerized anesthesia records. Comparison with voluntary reporting. *Anesthesiology* 1996; **85**: 977–87

15 Cooper JB. Is voluntary reporting of critical events effective for quality assurance? *Anesthesiology* 1996; **85**: 961–4

16 Cullen DJ, Bates DW, Small SD, Cooper JB, Nemeskal AR, Leape LL. The incident reporting system does not detect adverse drug events: a problem for quality improvement. *Jt Comm J Qual Improv* 1995; **21**: 541–8

17 Jayasuriya JP, Anandaciva S. Compliance with an incident report scheme in anaesthesia. *Anaesthesia* 1995; **50**: 846–9

18 Tiret L, Desmonts JM, Hatton F, Vourc'h G. Complications associated with anaesthesia–a prospective survey in France. *Can Anaesth Soc J* 1986; **33**: 336–44

19 Short TG, O'Regan A, Jayasuriya JP, Rowbottom M, Buckley TA, Oh TE. Improvements in anaesthetic care resulting from a critical incident reporting programme. *Anaesthesia* 1996; **51**: 615–21

20 Leape LL. Error in medicine. *JAMA* 1994; **272**: 1851–7

21 Schreiber PJ. Con: there is nothing wrong with old anesthesia machines and equipment. *J Clin Monit* 1996; **12**: 39–41

British Journal of Anaesthesia **89** (6)· 832–8 (2002)

Stereoselective *in vitro* degradation pattern of mivacurium in human plasma[†]

J. Laurin[1], F. Donati[2] and F. Varin[1]*

[1]*Faculté de Pharmacie, Université de Montréal C.P. 6128, Succ. Centre-Ville, Montréal (QC), Canada H3C 3J7.* [2]*Département d'Anesthésie, Faculté de Médecine, Université de Montréal C.P. 6128, Succ. Centre-Ville, Montréal (QC), Canada H3C 3J7*

**Corresponding author. E-mail: france.varin@umontreal.ca*

Background. Mivacurium is a mixture of three isomers, two of which are rapidly broken down *in vivo* by plasma cholinesterases. This study investigates the stereospecificity of mivacurium *in vitro* degradation to determine if it accounts for its *in vivo* behaviour.

Methods. The *in vitro* rate of degradation of each isomer of mivacurium and the *in vitro* rate of formation of their primary (monoesters and alcohols) and secondary (alcohols) metabolites were examined using human plasma from six healthy volunteers. The *in vitro* rate of degradation of the monoester metabolites was also assessed. All these determinations were made using a stereospecific high-performance liquid chromatography assay.

Results. The *in vitro* rate of disappearance of the two active isomers of mivacurium was very rapid, with mean values for the *trans trans* and *cis trans* isomers of 0.803 and 0.921 min^{-1} respectively. These values are twofold faster than published *in vivo* data. The *in vitro* rate of disappearance was much slower for the *cis cis* isomer, with a mean value of 0.0106 min^{-1}. The *cis trans* isomer was converted exclusively to *cis* monoester and *trans* alcohol, while only metabolites in the *trans* and *cis* configuration were found for the *trans trans* and *cis cis* isomers respectively. Mean *in vitro* rates of disappearance for the *trans* and *cis* monoester were 0.00750 and 0.000633 min^{-1} respectively.

Conclusions. The *in vitro* rates of hydrolysis of the active isomers of mivacurium confirm that plasma cholinesterases play a major role in their *in vivo* degradation, but that *in vivo* elimination is slowed by extravascular distribution. Mivacurium hydrolysis is stereoselective, the ester group in the *trans* configuration being more accessible to enzymatic attack. This stereoselective pattern, along with the relatively slow breakdown of the *cis cis* isomer, sheds light on the *in vivo* disposition of the *cis* alcohol metabolite.

Br J Anaesth 2002; **89**: 832–8

Keywords: blood, plasma; metabolism, mivacurium; metabolism, stereoselective; neuromuscular block, mivacurium

Accepted for publication: July 10, 2002

Mivacurium chloride consists of a mixture of three stereoisomers. The two most active are the *trans trans* and *cis trans* isomers (57 and 37% w/w respectively), which are equipotent; the *cis cis* isomer (6% w/w) has only one-tenth of the activity of the others in cats and monkeys.[1] Mivacurium isomers are believed to be hydrolysed mostly by plasma cholinesterases to give primary (monoester and alcohol) and secondary (alcohol) metabolites (Fig. 1).[2] The *in vivo* elimination half-life in humans is approximately 2 min for the *trans trans* and *cis trans* isomers and 30 min for the *cis cis* isomer.[3] The maximum plasma concentration of the metabolites is reached within 35 s of injection, with an average elimination half-life of 90 min. except for the *cis* alcohol, which is minimally and transiently detected.

Cook and colleagues[4] were the first to determine an *in vitro* degradation rate for the mixture of mivacurium but

---

[†]This research was supported by the Canadian Institutes of Health Research (MA-10274). A CIHR-Rx&D studentship was awarded to Julie Laurin.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

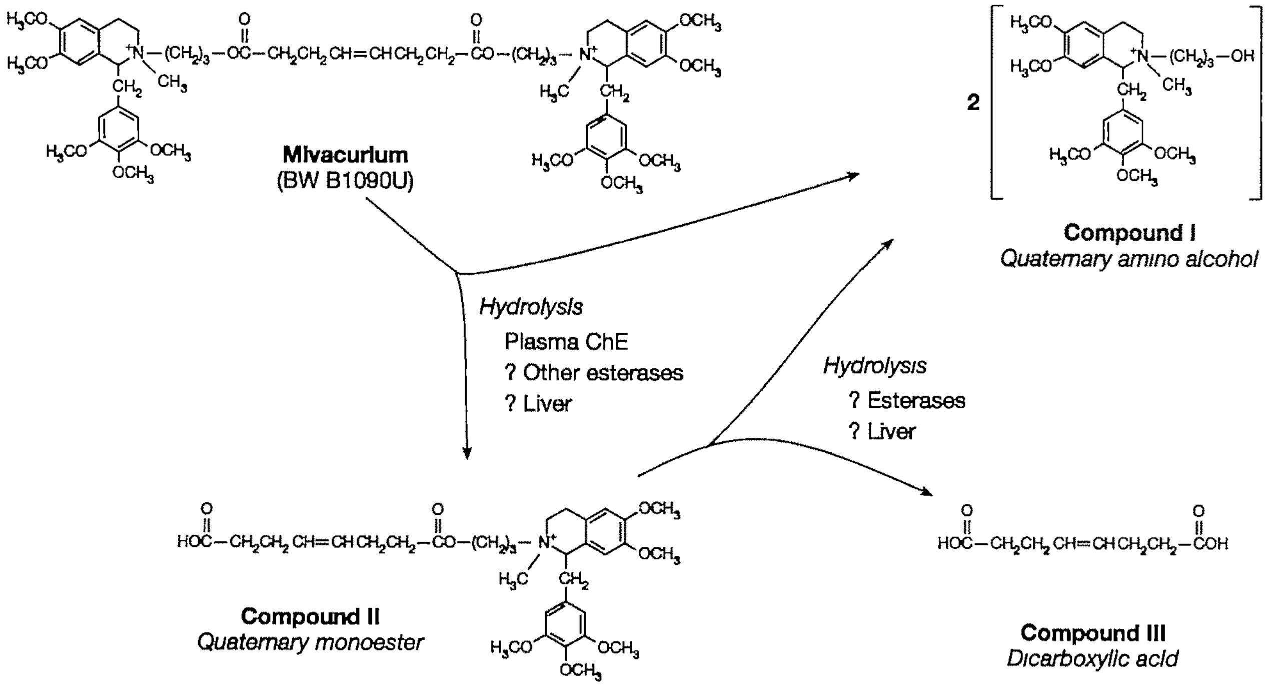


Fig 1 Putative degradation pathway of a mivacurium isomer. Reproduced from Savarese *et al.*, *Anesthesiology* 1998; **68** 723–33, with permission of the publisher.

their assay was not stereoselective. Referring to a personal communication, Lien and colleagues[5] reported an *in vitro* half-life for the individual isomers (0.83, 1.30 and 276 min for the *trans trans*, *cis trans* and *cis cis* isomers respectively). However, it is unclear whether the isomers were incubated individually or as a mixture. Wiesner and colleagues[6] have recently reported shorter *in vitro* half-lives of 0.71 and 0.61 min for the *trans trans* and *cis trans* isomers respectively after incubation of the mixture. These studies did not determine the concentrations of metabolites and therefore the actual pathway of their metabolite formation remains to be elucidated.

The present study was designed to elucidate the individual degradation pathways of each isomer of mivacurium and its monoester metabolites in human plasma, and represents the first attempt to propose an overall pattern for the *in vivo* disposition of mivacurium.

Methods

Chemicals

The three isomers of mivacurium chloride, the monoester and quaternary alcohol metabolites, and laudanosine were provided by Glaxo Wellcome (Research Triangle Park, NC, USA). All analytes were supplied individually with the exception of the monoester metabolite standard, which was supplied as a mixture of the *cis* and *trans* isomers. The relative proportions of the *cis* and *trans* monoester isomers in the mixture were reported by the supplier to be approximately 26.3 and 66.3% respectively. All organic solvents were HPLC (high-performance liquid chromatography) grade (Anachemia, Montreal, Canada). Echothiophate iodide, a plasma cholinesterase inhibitor, was supplied by Wyeth-Ayerst Laboratories (Montreal, Canada).

Plasma collection

Blood was obtained from six healthy fasting volunteers after they had given written informed consent. The study protocol was approved by the Hotel-Dieu Hospital Ethics Committee (Montreal, Canada). Among the volunteers, there were three men and three women and their age varied between 23 and 40 yr. Approximately 100 ml of blood was obtained in a heparinized syringe. After collection, the blood was centrifuged at 1650 *g* for 15 min and the plasma was separated and kept on an ice-water bath until incubation.

Incubation

The three isomers of mivacurium and the mixture of monoester metabolites were incubated separately at 37°C in fresh plasma obtained from every volunteer. The *in vitro* study was performed within 1 h of blood collection to ensure integrity of the medium, especially with respect to enzyme activity. For each analyte, a starting solution (10 ml) was prepared by adding an appropriate amount of corresponding analyte to each preincubated individual plasma. Final concentrations of 4500 ng ml^{-1} (4.37 μmol $litre^{-1}$) for

Table 1 Comparison of *in vitro* and *in vivo* parameters. The $k_{\mathrm{in\ vitro}}$ values are mean (SD). The $T_{\frac{1}{2}\ \mathrm{in\ vivo}}$ values are taken from reference 3

Variable	**Mivacurium**			**Monoester**	
	trans trans	*cis trans*	*cis cis*	*trans*	*cis*
$k_{\mathrm{in\ vitro}}$ (min^{-1})	0.803 (0.142)	0.921 (0.0634)	0.0106 (0.00176)	0.00750 (0.00116)	0.000633 (0.000242)
$T_{\frac{1}{2}\ \mathrm{in\ vitro}}$ (min)	0.890	0.756	67.2	94.0	1220
$T_{\frac{1}{2}\ \mathrm{in\ vivo}}$ (min)	2.4	2.0	28.5	86.3	100

trans trans mivacurium, 2500 ng ml^{-1} (2.43 µmol litre^{-1}) for *cis trans* mivacurium, 500 ng ml^{-1} (0.49 µmol litre^{-1}) for *cis cis* mivacurium and 3000 ng ml^{-1} (5.15 µmol litre^{-1}) for monoester metabolites were prepared. These final concentrations were chosen to mimic the maximum plasma concentrations observed in patients after an intubating dose of the commercial mixture of the three isomers.[3] According to the relative proportions of the *trans* and *cis* monoester in the mixture, the monoester metabolite starting solution corresponded to 1989 ng ml^{-1} (3.41 µmol litre^{-1}) and 789 ng ml^{-1} (1.35 µmol litre^{-1}) of *trans* and *cis* monoester respectively. Each starting solution was separated in nine aliquots of 1 ml, to which 20 µl of echothiophate iodide 0.04 M was added at predetermined times to stop the reaction and to prevent further degradation of the compound. The time points for stopping the reaction after addition of the analyte were 0, 1, 2, 3, 4, 5, 6, 7 and 8 min for the *trans trans* and *cis trans* mivacurium metabolites; 0, 15, 30, 45, 60, 75, 90, 105 and 120 min for the *cis cis* mivacurium metabolites; and 0, 60, 120, 180, 240, 300, 360 and 420 min for the monoester metabolites. After adding the inhibitor, the aliquots were frozen using dry ice and then stored at –70°C until HPLC analysis.

Sample preparation and chromatographic apparatus and conditions

Mivacurium isomers and their metabolites were determined by HPLC using a method similar to that published for the determination of cisatracurium and its metabolites in human urine.[7] Bond Elut phenyl solid-phase extraction cartridges (Varian, Harbor City, CA, USA) were conditioned with acetonitrile 1 ml and 5 mM sulphuric acid 1 ml. The plasma sample (0.75 ml) and internal standard (75 µl of laudanosine 1 µg ml^{-1}) were combined in the reservoir and then aspirated through the sorbent. A vacuum of 50–80 kPa was applied to the manifold of the Vac-Elut chamber (Analytichem International, Harbor City, CA, USA) throughout the extraction procedure. The cartridges were washed sequentially with 5 mM sulphuric acid 0.75 ml and a mixture of methanol:water (50:50, 0.75 ml). Analytes were eluted with 80 mM sodium sulphate 2×300 µl in 5 mM sulphuric acid:acetonitrile (40:60). The eluents were then reduced to half of their volume by evaporation using a Speed-Vac concentrator (Model SC210A; Savant Instruments, Farmingdale, NY, USA). Aliquots were injected directly into the HPLC system according to the following procedure.

The chromatographic system consisted of a Constametric 4100 pump (LDC Analytical, Riviera Beach, FL, USA) which was programmed to deliver 14 mM sodium sulphate in 0.5 mM sulphuric acid:acetonitrile (40:60) for 5 min followed by 70 mM sodium sulphate in 0.5 mM sulphuric acid:acetonitrile (40:60) for 6 min, returning to the initial condition to re-equilibrate for 3 min. The flow rate was 2.0 ml min^{-1} and the mobile phase was not allowed to recirculate. Samples were injected using an auto-injector (SIL-9A; Shimadzu, Kyoto, Japan). Separation of mivacurium isomers and their metabolites was performed on a 5 µm Spherisorb strong cation exchanger column (150×4.6 mm internal diameter; Phenomenex, Torrance, CA, USA). Peaks were detected with a Hewlett Packard 1046 A fluorescence detector (Hewlett Packard, Waldbroom, Germany) at excitation and emission wavelengths of 202 and 320 nm respectively. A Shimadzu C-R3A integrator was used.

The method proved to be sensitive, with a lower limit of quantitation of 4.88 ng ml^{-1} (0.0047 µmol litre^{-1}) for each isomer of mivacurium and for the quaternary alcohol metabolites, and 10.36 ng ml^{-1} (0.0232 µmol litre^{-1}) and 4.11 ng ml^{-1} (0.0071 µmol litre^{-1}) for the *trans* and *cis* monoesters respectively. The assay proved to be linear up to 5000 ng ml^{-1} (4.86 µmol litre^{-1}) for the isomers of mivacurium, 5000 ng ml^{-1} (11.20 µmol litre^{-1}) for the quaternary alcohol metabolites, 2652 ng ml^{-1} (4.55 µmol litre^{-1}) for the *trans* monoester and 1052 ng ml^{-1}(1.81 µmol litre^{-1}) for the *cis* monoester. The coefficient of determination (r^2) was always higher than 0.9930 for each analyte. The method proved to be reproducible for each analyte, with a coefficient of variation always less than 20% over the linear range.

Data analysis

The rate of *in vitro* disappearance ($k_{\mathrm{in\ vitro}}$) of each analyte from human plasma was determined by fitting the plasma data to a non-compartmental model with bolus input using a non-linear least-squares computer program (WinNonlin® software; Pharsight Scientific Consulting, Palo Alto, CA, USA) that applied linear regression to all data points. The *in vitro* elimination half-life ($T_{\frac{1}{2}\ \mathrm{in\ vitro}}$) was calculated using 0.693 $k_{\mathrm{in\ vitro}}{}^{-1}$. The mass balance (number of moles

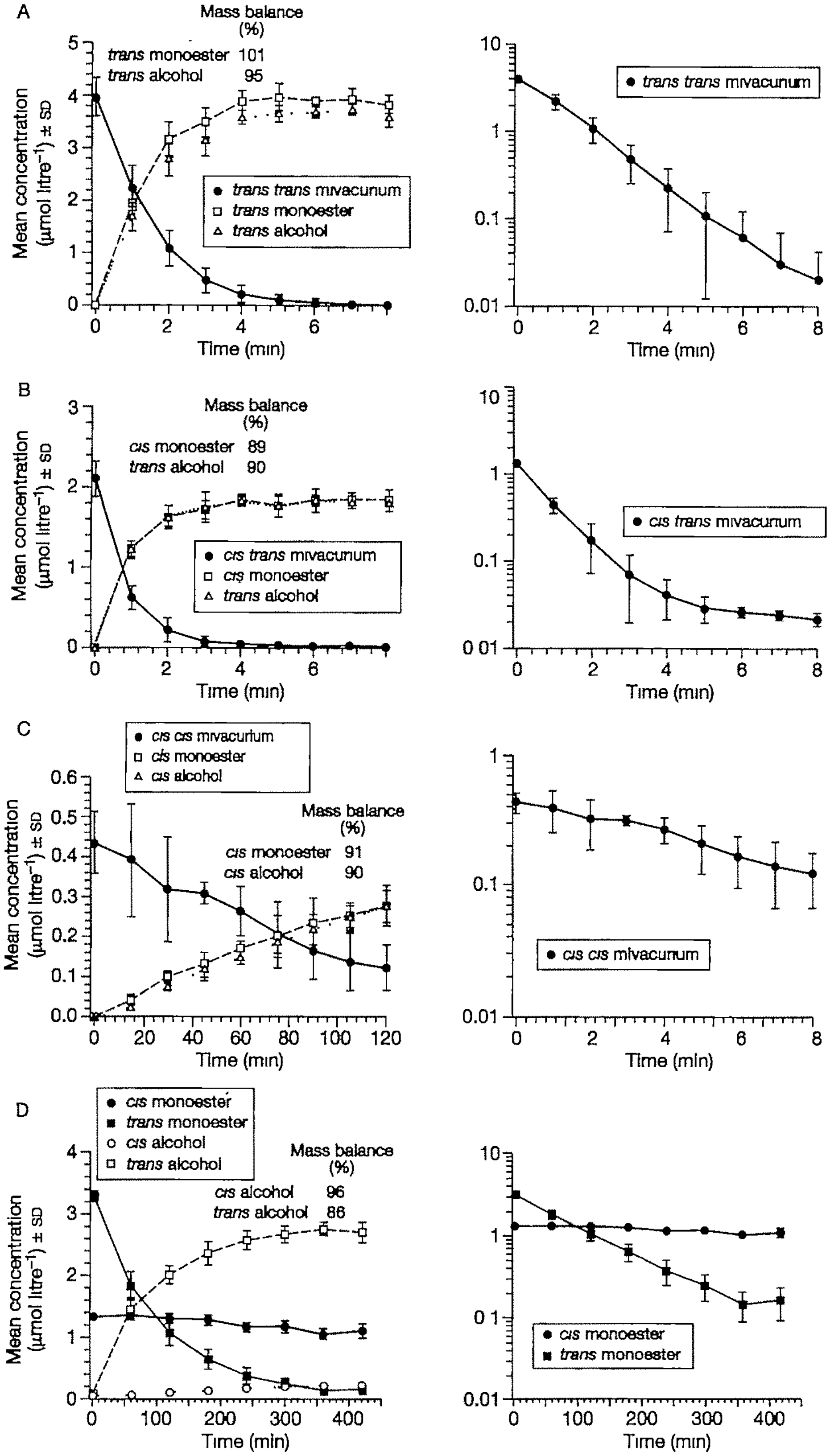


Fig 2 *In vitro* degradation in human plasma after separate incubation of the (A) *trans trans*, (B) *cis trans* and (C) *cis cis* isomers of mivacurium and (D) a mixture of the *cis* and *trans* monoesters. The left panels illustrate the mass balance between the degradation of parent compound and the formation of metabolites on an ordinal scale. The right panels illustrate the exponential decline of the plasma concentration–time profile for the parent compound.

disappeared *vs* number of moles formed) was examined in all subjects.

Results

After incubation in human plasma, *trans trans* mivacurium disappeared very rapidly, with a mean $k_{\text{in vitro}}$ value of 0.803 min^{-1} (Table 1). This isomer was completely and equally (on a molar basis) converted to *trans* monoester and *trans* alcohol metabolites (Fig. 2A).

The disappearance of *cis trans* mivacurium from human plasma was also very rapid, with a mean $k_{\text{in vitro}}$ value of 0.921 min^{-1} (Table 1). Moreover, the hydrolysis reaction was almost complete at 4 min, when about 98% of the *cis trans* mivacurium was degraded. Figure 2B shows that the plasma concentrations of *cis trans* mivacurium and its corresponding metabolites did not change significantly after 4 min of incubation. The individual $k_{\text{in vitro}}$ values were therefore calculated between 0 and 4 min. Our results also show that *cis trans* mivacurium is almost exclusively converted to *cis* monoester and *trans* alcohol. Although we were able to quantify some *cis* alcohol after the incubation of the *cis trans* isomer, less than 1% of the *cis trans* isomer was converted into *cis* alcohol after 8 min. This finding is consistent with the 2% fraction of the *cis trans* isomer that was not hydrolysed after 4 min. This was considered to be negligible and within the error of the assay, and the data are therefore not presented in the tables and figures.

After incubation in human plasma, the *cis cis* isomer of mivacurium disappeared at a much slower rate than that of the other two isomers. After 120 min of incubation, the hydrolytic reaction was incomplete, with 30% of the initial *cis cis* mivacurium plasma concentration remaining. Only metabolites in the *cis* configuration resulted from hydrolysis of this isomer. Hence, this isomer was equally (on a molar basis) converted to *cis* monoester and *cis* alcohol metabolites (Fig. 2C). The resulting mean $k_{\text{in vitro}}$ value was 0.0106 min^{-1} (Table 1).

After a 7-h incubation, the *trans* monoester metabolite was completely converted to *trans* alcohol metabolite, whereas only 20% of the *cis* monoester metabolite was converted to *cis* alcohol metabolite (Fig. 2D). The resulting mean $k_{\text{in vitro}}$ value was 0.00750 min^{-1} for the *trans* monoester metabolite and 0.000633 min^{-1} for the *cis* monoester metabolite (Table 1). The mean terminal elimination half-life ($T_{\frac{1}{2}\text{ in vivo}}$) obtained in eight healthy patients undergoing elective surgery[2] is also presented in Table 1 for each isomer of mivacurium and for the monoester metabolites.

As demonstrated in Figure 2, the mass balance (number of moles disappeared *vs* number of moles formed) was good, the values varying from 86 to 101%. The slight variation was probably the result of the error inherent in the analytical method (±15%).

In view of these results, a pattern is proposed for the stereoselective degradation of mivacurium (Fig. 3).

Discussion

Mivacurium is an ester type of neuromuscular blocking agent and therefore undergoes enzymatic breakdown by plasma cholinesterases. Because mivacurium contains two ester groups, enzymatic breakdown can occur at either one of these sites. Thus, the hydrolysis of one mole of mivacurium will result in the formation of one mole of monoester metabolite and one mole of alcohol metabolite. Theoretically, when mivacurium is in the *trans trans* or *cis cis* geometrical configuration, the metabolites will be in either the *trans* or the *cis* configuration respectively if there is no interconversion *in vivo*. Our results support the

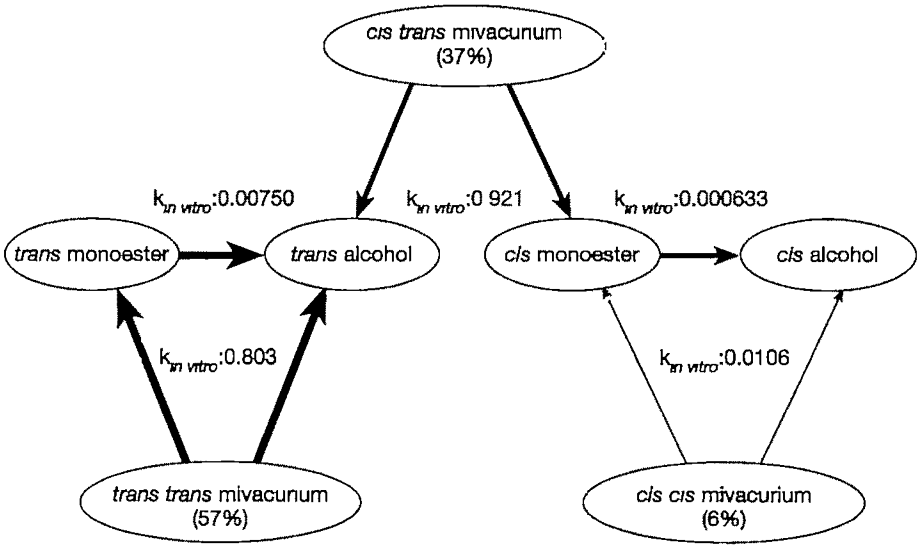


Fig 3 Stereoselective degradation pattern of mivacurium. Note the very slow breakdown of *cis* monoester to *cis* alcohol.

absence of *in vivo* interconversion. On the other hand, when mivacurium is in the *cis trans* configuration, metabolites could be in the *cis* or *trans* configuration. More specifically, if the ester group in the *trans* configuration is attacked, it will lead to the formation of *trans* alcohol and *cis* monoester. Therefore, the hydrolysis of *cis trans* mivacurium could theoretically result in the formation of the *trans* alcohol and *cis* monoester metabolites and/or the *cis* alcohol and *trans* monoester metabolites. Our results show clearly that *cis trans* mivacurium is converted exclusively to *trans* alcohol and *cis* monoester metabolites, suggesting that the ester group of the isomer in the *trans* configuration is more labile.

There is no clear explanation for the flattening of the curve for *cis trans* degradation in plasma. However, we are sure that this finding is not an artefact. There are two good reasons why analytical sensitivity can be ruled out. First, the levels are well above the lower limit of quantitation (LLOQ; at least four times the LLOQ). Secondly, the flattening of the *cis trans* concentration curve was consistent in all patients but never observed for the *trans trans* isomer. After 4 min, the measured plasma concentration of the *cis trans* isomer averaged 50 ng ml^{-1} (0.0486 μmol $litre^{-1}$), which represents approximately 2% of the initial concentration. One possible explanation for the flattening of the curve would be that the rate of ester hydrolysis is different for the *cis* and *trans* positions. Hydrolysis at the *trans* position would be complete at 4 min and the flattening of the curve could be attributed to slower hydrolysis at the *cis* position.

After the hydrolysis of mivacurium isomers into monoester and alcohol metabolites, the monoester metabolites are in turn degraded into alcohol metabolites. However, as the $k_{\text{in vitro}}$ values for the monoesters are at least 10-fold slower than those for the isomers, the relative importance of this secondary metabolic pathway to the formation of the alcohol metabolite is thought to be negligible.

Our results also show that the *cis* monoester metabolite does not undergo any significant *in vitro* hydrolysis in comparison with the *trans* monoester metabolite. This finding supports the results obtained for the isomers, i.e. that the ester group in the *trans* configuration is more susceptible to attack by the enzyme. The presence of greater steric hindrance when the ester group is in the *cis* configuration may explain the greater resistance to enzymatic degradation.

For drugs undergoing extensive hydrolysis in human plasma (non-organ-based elimination), the *in vitro* rate of degradation ($k_{\text{in vitro}}$) is often used as a substitute in pharmacokinetic models assuming peripheral elimination.[8–10] In addition, direct comparison of *in vitro* and *in vivo* elimination half-lives provides information about the relative contribution of organ-based elimination (e.g. by the kidneys and liver) to the overall body elimination. Our results indicate that, for the two most active isomers (*trans trans* and *cis trans*), the $T_{\frac{1}{2}\text{ in vitro}}$ is 2-fold faster than the $T_{\frac{1}{2}\text{ in vivo}}$, confirming that hydrolysis by plasma cholinesterases plays a major role in the degradation of these two isomers. The possibility that this apparent discrepancy resulted from the fact that two different populations of subjects were studied cannot be ruled out. However, Wiesner and colleagues[6] recently reported *in vitro* half-lives similar to those obtained in this study. Another explanation for the slower *in vivo* elimination could be that extravascular distribution of these two isomers delays their overall elimination from the body. The presence of plasma cholinesterases in the cerebrospinal fluid has been demonstrated in animals,[11] although their activity may differ markedly between tissues and plasma. Despite the fact that the two active isomers of mivacurium (*trans trans* and *cis trans*) are eliminated rapidly by plasma cholinesterases, a contribution of the peripheral compartment to their elimination cannot be excluded. Recent data have confirmed the presence of an arterial–venous gradient of approximately 30% across muscle tissue in anaesthetized patients.[12]

In contrast, the $T_{\frac{1}{2}\text{ in vivo}}$ for the *cis cis* isomer is approximately 2-fold faster than the $T_{\frac{1}{2}\text{ in vitro}}$. This finding is an indication that the overall elimination of this isomer is not solely the result of its hydrolysis by plasma cholinesterases. Indeed, the contribution of renal function to the overall elimination of this isomer has been demonstrated by Head-Rapson and colleagues.[13] Moreover, Lien and colleagues[5] have shown that the clearance of this isomer is not related to plasma cholinesterase activity.

For the monoester metabolites, the *in vivo* and *in vitro* values were similar for the *trans* monoester, indicating a minor contribution of organ-based elimination to total body disposition. Conversely, the *in vitro* half-life of the *cis* monoester was considerably slower than that observed *in vivo*. However, this value should be interpreted cautiously as the duration of incubation did not allow accurate determination of the half-life. Nonetheless, our findings suggest that the contribution of enzymatic hydrolysis to the overall *in vivo* elimination of the *cis* monoester metabolite is negligible.

When examining the *in vivo* formation and elimination of the alcohol and monoester metabolites after an i.v. bolus of the commercial mixture of mivacurium in human patients, Lacroix and colleagues[3] noted that the *cis* alcohol metabolite was detected minimally and transiently. An initial mixing peak was observed at approximately 30 s for both the *cis* and the *trans* alcohol metabolite. This was attributed to the alcohols (known degradation or synthesis by-products of the isomers) that are already contained in the injectable solution. Of importance, the levels of the *cis* alcohol were not quantifiable (below the LLOQ) after only 8 min, while levels almost 10-fold higher allowed characterization of the kinetics of the *trans* alcohol for up to 250 min. As the later portion of the plasma concentration–time curve was more compatible with *in vivo* formation of the metabolites, no explanation can be provided for this finding. Our *in vitro* results now shed some light on the *in vivo* disposition of the *cis* alcohol metabolite. First, less than 2% of the *cis* alcohol is formed after *in vitro* degradation of the *cis trans* isomer. Secondly, the *in vitro* rate of formation of *cis* alcohol from the *cis* monoester is questionable. Finally, as the *cis cis* isomer represents only 6% of the injectable mixture of mivacurium, its contribution to the *in vivo* formation of the *cis* alcohol is certainly minimal.

In conclusion, the *in vitro* rates of hydrolysis of the active isomers confirm that plasma cholinesterases play a major role in their *in vivo* degradation, but also suggest that their *in vivo* elimination is slowed by extravascular distribution. Mivacurium hydrolysis is stereoselective, the *trans* configuration being more amenable to ester hydrolysis than the *cis* configuration. This stereoselective pattern, along with the relatively slow breakdown of the *cis cis* isomer, explains the *in vivo* disposition of the *cis* alcohol metabolite. Hydrolysis is facilitated by the presence of another esterified moiety at the opposite end of the molecule, the hydrolysis of the *cis cis* and *trans trans* isomers being considerably faster than that of their respective monoesters. From the results of this *in vitro* study we propose an overall stereoselective pattern for the degradation of mivacurium that allows the contribution of organ-based elimination to be dissociated from that of non-organ-based elimination.

Acknowledgements

The authors would like to thank Louisa Cale and Johanne Couture for their technical assistance

References

1 Belmont MR, Beemer G, Bownes P, Russo J, Wisowaty J, Savarese JJ. Comparative pharmacology of mivacurium and isomers in rhesus monkeys [abstract]. *Anesth Analg* 1993; **76**: S18

2 Savarese JJ, Hassan HA, Salvatore JB, *et al.* The clinical neuromuscular pharmacology of mivacurium chloride (BW B1090U). *Anesthesiology* 1988; **68**: 723–32

3 Lacroix M, Donati F, Varin F. Pharmacokinetics of mivacurium isomers and their metabolites in healthy volunteers after intravenous bolus administration. *Anesthesiology* 1997, **86**: 322–30

4 Cook DR, Stiller RL, Weakly JN, Chakravorti S, Brandom BW, Welch RM. *In vitro* metabolism of mivacurium chloride (BW B1090U) and succinylcholine. *Anesth Analg* 1989; **69**: 452–6

5 Lien CA, Schmith VDE, Embree PB, Belmont MR, Wargin WA, Savarese JJ The pharmacokinetics and pharmacodynamics of the stereoisomers of mivacurium in patients receiving nitrous oxide/opioid/barbiturate anesthesia. *Anesthesiology* 1994; **80**: 1296–306

6 Wiesner G, Gruber M, Keyl C, Schneider A, Drescher J, Hobbhahn J. *In vitro* effects of fluoride on pseudocholinesterase activity and the metabolism of the cis-trans and trans-trans isomers of mivacurium. *Anesthesiology* 2001; **95**: 806–7

7 Bryant BJ, James CD Jr, Cook DR, Harrelson JC. High performance liquid chromatography assay for cisatracurium and its metabolites in human urine. *J Liquid Chromatogr Relat Technol* 1997; **20**: 2041–51

8 Fisher DM, Canfell PC, Fahey MR, *et al.* Elimination of atracurium in humans: Contribution of Hofmann elimination and ester hydrolysis versus organ-based elimination. *Anesthesiology* 1986; **65**: 6–12

9 Tran TV, Fiset P, Varin F. Pharmacokinetics and pharmacodynamics of cisatracurium after a short infusion in patients under propofol anesthesia. *Anesth Analg* 1998; **87**: 1158–63

10 Bergeron L, Bevan DR, Berrill A, Kahwaji R, Varin F. Concentration–effect relationship of cisatracurium at three different dose levels in the anesthetized patient. *Anesthesiology* 2001; **95**: 314–23

11 Ummenhofer WC, Brown SM, Bernards CM. Acetylcholinesterase and butyrylcholinesterase are expressed in the spinal meninges of monkeys and pigs. *Anesthesiology* 1998; **88**: 1259–65

12 Ezzine S, Donati F, Varin F. Mivacurium arteriovenous gradient during steady state infusion in anesthetized patients. *Anesthesiology* 2002; **97**: 622–9

13 Head-Rapson AG, Devlin JC, Parker CJR, Hunter JM. Pharmacokinetics and pharmacodynamics of the three isomers of mivacurium in health, in end-stage renal failure and in patients with impaired renal function. *Br J Anaesth* 1995; **75**· 31–6

British Journal of Anaesthesia **89** (6) 839–45 (2002)

Pharmacogenetics of codeine metabolism in an urban population of children and its implications for analgesic reliability

D. G. Williams[1 2], A. Patel[3] and R. F. Howard[4]*

[1]Anaesthetic Department, The Royal London Hospital, Whitechapel, London E1 1BB, UK. [2]Portex Department of Anaesthesia, Institute of Child Health, Guilford Street, London WC1N 1EH, UK. [3]Anaesthetic Department, The Royal National Throat, Nose and Ear Hospital, Grays Inn Road, London WC1X 8DA, UK. [4]Department of Anaesthesia, Great Ormond Street Hospital for Children NHS Trust and Children Nationwide Pain Research Centre, Great Ormond Street, London WC1N 3JN, UK

**Corresponding author. E-mail: r.howard@ich.ucl.ac.uk*

Background. Codeine analgesia is wholly or mostly due to its metabolism to morphine by the cytochrome P450 enzyme CYP2D6, which shows significant genetic variation in activity. The aims of this study were to investigate genotype, phenotype and morphine production from codeine in children undergoing adenotonsillectomy, and to compare analgesia from codeine or morphine combined with diclofenac.

Methods. Ninety-six children received either codeine 1.5 mg kg^{-1} or morphine 0.15 mg kg^{-1} in a randomized, double-blind design. Genetic analysis was performed and plasma morphine concentrations at 1 h were determined. Postoperative analgesia and side-effects were recorded.

Results. Forty-seven per cent of children had genotypes associated with reduced enzyme activity. Mean (SD) morphine concentrations were significantly lower ($P<0.001$) after codeine [4.5 (0.3) ng ml^{-1}] than after morphine [24.7 (1.5) ng ml^{-1}], and morphine and its metabolites were not detected in 36% of children given codeine. There was a significant relationship between phenotype and plasma morphine ($P=0.02$). More children required rescue analgesia after codeine at both 2 ($P<0.05$) and 4 h after administration ($P<0.01$). Fifty-six per cent of children vomited after morphine and 29% after codeine ($P<0.01$). Neither phenotype nor morphine concentration was correlated with either pain score or the need for rescue analgesia ($r=-0.21$, 95% confidence interval –0.4, –0.01).

Conclusions. Reduced ability for codeine metabolism may be more common than previously reported. Plasma morphine concentration 1 h after codeine is very low, and related to phenotype. Codeine analgesia is less reliable than morphine, but was not well correlated with either phenotype or plasma morphine in this study.

Br J Anaesth 2002; **89**: 839–45

Keywords: analgesia, genetic factors; analgesics opioid, codeine; enzymes, cytochrome P450 CYP2D6; surgery, adenotonsillectomy

Accepted for publication: July 8, 2002

Codeine is still widely prescribed for postoperative pain relief and is frequently recommended for paediatric use.[1 2] The reputedly lower incidence of opioid-related side-effects has made codeine popular for younger age groups, including neonates, especially in situations where airway management and neurological assessment are critical.[3–5] However, there is some doubt about the efficacy and reliability of codeine.[6] Both animal and adult human laboratory experimental studies have shown that there is significant variability in both the pharmacokinetics and pharmacodynamics of codeine. These studies also suggest that the analgesic effect of codeine is either wholly or mostly dependent on its metabolism to morphine.[6 7] Metabolism of codeine to morphine is catalysed by the cytochrome P450 enzyme CYP2D6. Over 50 different genetic variants are known to exist for CYP2D6, which leads to a wide spectrum of

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

metabolic capabilities within populations.[8 9] Individuals are normally classified as either poor metabolizers (PM) or extensive metabolizers (EM), depending on the activity of the enzyme, although this is known to be an oversimplification. PMs will produce little or no morphine from codeine whereas EMs will produce morphine, although the actual amount may show wide variation.[10–12]

The aims of the current studies were to investigate: (i) genotype, phenotype and morphine production from codeine in a UK urban population of children undergoing adenotonsillectomy; and (ii) the efficacy, reliability and side-effects of codeine as part of a postoperative analgesic regimen.

Methods

All procedures were carried out at the Royal National Throat, Nose and Ear Hospital, London. After obtaining local research ethics committee approval, we recruited 98 children aged from 3 to 12 yr, ASA I and II, undergoing adenotonsillectomy. Informed written parental consent was sought for each child before enrolment in the study. The children were randomized into two groups: group C received codeine 1.5 mg kg^{-1} and group M morphine 0.15 mg kg^{-1} i.m. shortly after the induction of anaesthesia. Both groups also received diclofenac 1 mg kg^{-1} per rectum at the same time. Blood for analysis was taken from an i.v. cannula inserted for the procedure. After induction, 2–4 ml blood was collected for genetic analysis, and a further 1–2 ml was taken 1 h after injection of the study drug for the measurement of plasma morphine and morphine metabolites.

Surgery was performed using electrocautery for tonsillar dissection and haemostasis. The anaesthetist and surgeon present varied depending on which day and on which operating list the procedure was performed. All staff involved in the procedure and the perioperative care of the child were blinded as to which opioid was administered.

No premedication was given. Topical local anaesthesia to facilitate i.v. cannulation was applied before anaesthesia, which was induced either by the i.v. route (propofol 2–5 mg kg^{-1}) or by inhalation (oxygen, nitrous oxide and sevoflurane). Once adequate anaesthesia had been established, a laryngeal mask of appropriate size was inserted into the airway. Anaesthesia was maintained with oxygen, nitrous oxide and sevoflurane with spontaneous ventilation. Analgesia (study drug plus diclofenac) was administered as soon as convenient after induction. Hartman's solution 10 ml kg^{-1} was given during the procedure and continued into the postoperative period at a maintenance rate appropriate to each individual child. At the end of the procedure the patient was allowed to breathe 100% oxygen, and the laryngeal mask was removed once airway reflexes had returned. Patients were kept in the recovery area until they were awake and comfortable and able to return to the ward. Further analgesia was not given during the procedure unless indicated on the basis of clinical judgement. Ondansetron 0.1–0.2 mg kg^{-1} was administered if required.

The analysis was performed at the Department of Molecular Biology at University College London. Whole blood was stored at –70°C until analysis and all the samples were processed in one batch. DNA was extracted from the whole blood, which was then split using a two-stage polymerase chain reaction (PCR). The PCR products were labelled fluoroscopically to allow detection electronically using an ABI-377 analyser (Applied Biosystems, Foster City, CA, USA). Over 50 variants of the CYP2D6 gene have been identified and most are classified as rare, 87% of genotypes being accounted for by five variants.[9 13] It is impractical to look for all these different variants in each sample of DNA; thus, the most common polymorphisms causing alteration in enzyme activity were targeted. These were CYP2D6*1, *2, *3, *4, *5, *9, *10 and *17. CYP2D6*1 is considered the normal or wild-type gene and has normal activity. Variants *3, *4, *5 and *9 have no activity and account for over 90% of PMs, whilst *2, *10 and *17 have reduced activity. Four possible phenotypes were identified. If a patient was homozygous for polymorphisms known to show no activity, he or she was classified as a PM, whilst a combination of a polymorphism of reduced activity with one of no activity classified the patient as an intermediate/poor metabolizer (IM/PM). An intermediate metabolizer (IM) was a patient with either a combination of two polymorphisms with reduced activity or a combination of one normal polymorphism with one of no activity, and an extensive metabolizer (EM) was a patient who was either homozygous for the normal gene or who had a combination of a normal polymorphism with one of reduced activity. Genotyping identified all the polymorphisms apart from *1 so, if none was found, the sample was considered to be from a patient with the normal gene. Thus, there was a chance that a PM patient with another polymorphism could have been considered an EM (false negative), though as these polymorphisms are rare the estimated risk of this occurrence was very small.

For measurement of plasma morphine and metabolites, the blood samples were centrifuged at 3000 r.p.m. for 10 min within 15 min of being taken. The plasma was stored before processing at –70°C. Plasma morphine and its glucuronide metabolites were measured by high-performance liquid chromatography at the Institute of Child Health, London. Analysis of the samples was in two batches, and limits of detection were 5 (SD 2) ng ml^{-1} for morphine and 10 (2) ng ml^{-1} for morphine-6-glucuronide (M6G) in both. The coefficient of variation for morphine was 4% at 20 ng ml^{-1}. The limit of detection for morphine-3-glucuronide (M3G) was 30 (8) ng ml^{-1} in the first batch and 60 (8) ng ml^{-1} in the second.

Time to first analgesia (time from the injection of the opioid to the first dose of supplementary analgesia) and pain scores (using self-report and behavioural pain assessment tools) both at rest and on swallowing were used to assess

Table 1 Patient characteristics for the codeine and morphine groups. Data are mean (SD or range) or number *P=0.044

	Codeine group (n=48)	**Morphine group (n=48)**
Sex (male/female)	24/24	23/25
Age (yr)	7.31 (3–12)	6.23 (3–12)
Weight* (kg)	32.39 (19.2)	25.79 (11.49)
Surgical time (min)	33.52 (10.7)	33.06 (11.48)
Caucasian	21	15
Asian	12	10
Afro-Caribbean	5	11
Turkish	5	3
Arab	0	2
Caucasian/Asian	3	1
Caucasian/Afro-Caribbean	1	4
Caucasian/Arab	1	1
Asian/Afro-Caribbean	0	1

Table 2 Ethnicity in relation to phenotype. Data are numbers of patients. EM=extensive metabolizer; IM=intermediate metabolizer; IM/PM =intermediate/poor metabolizer, PM=poor metabolizer

	EM	**IM**	**IM/PM**	**PM**
Caucasian	13	15	7	1
Asian	12	5	2	2
Afro-Caribbean	8	3	5	
Turkish	3	2	3	
Arabian	1	1		
Caucasian/Asian	4			
Caucasian/Afro-Caribbean	3	2		
Caucasian/Arabian	1			1
Asian/Afro-Caribbean		1		

Table 3 Phenotype distribution (type of metabolizer)

Phenotype	**Morphine group (n=48)**	**Codeine group (n=48)**
Poor	2	2
Intermediate/poor	8	9
Intermediate	12	17
Extensive	26	19

analgesia. The need for extra analgesia was assessed on clinical grounds by the anaesthetist and/or the nurse responsible for the patient. Further analgesia was given as an i.v. bolus of morphine 20 μg kg^{-1}, oral morphine solution 0.1 mg kg^{-1} or oral acetaminophen 20 mg kg^{-1} at their discretion and the patient was subsequently excluded from the analysis.

Two methods of pain scoring were used, both of which have been verified in this age group. A 'faces' type self-reporting pain tool[14] was used in the recovery ward at the time of blood sampling for measurement of plasma morphine concentrations and 1, 2, 3 and 4 h after the end of the procedure, and the Children's Hospital of Eastern Ontario Pain Score (CHEOPS)[15] in the recovery ward. The scores were taken at each time point, both at rest and on swallowing, to provide static and dynamic measures of analgesia. The children were introduced to the self-reporting pain scale at the preoperative visit and shown how to use it. All nursing staff involved in the care of the children enrolled in the study had been taught previously how to use both pain scores.

Respiratory rate and a five-point sedation score (1=awake, 5=hard to rouse) were also recorded at the same time points as above. Postoperative vomiting was assessed by counting the number of vomiting episodes for each patient in a number of set time periods (<1, 1–2, 2–4 and 4–8 h). Again, patients were removed from analysis once further analgesia had been administered. Other unexpected complications and adverse effects were also recorded. Patients were monitored closely until discharge from the hospital.

All data were handled electronically and calculations performed using either Microsoft Excel 2000 or Graphpad Prism 3.0. Comparisons between continuous variables were made using either analysis of variance with Bonferroni post-test corrections or t-tests as appropriate. Survival analysis was performed using Kaplan–Meier survival curves. Categorical data were analysed using the χ^2 test and correlation between independent variables was tested with Pearson's correlation coefficient. For all comparisons, $P<0.05$ was considered significant.

Results

Ninety-eight children were recruited into the study but two were excluded: one child was given an incorrect dose of the study opioid, and consent for the other was withdrawn after the procedure had been postponed on the first attendance. Data were therefore included from a total of 96 patients; of these, 48 received morphine and 48 received codeine.

Patient characteristics are shown in Table 1. There was no significant difference between the two groups for age, sex or duration of surgery, or in the make-up of the ethnic groups of the patients randomized to the two arms of the study.

The total number of patients with phenotypes indicating reduced enzyme activity (PM, IM/PM and IM) in the study population was 46 (47%). The total number of PMs, who would not be expected to produce morphine from codeine at all, was 4 (4.1%). The distribution of these phenotypes in each ethnic group and in the two respective treatment groups is shown in Tables 2 and 3.

One sample from group C was lost by the laboratory. Results of the measurement of plasma concentrations of morphine and its glucuronide metabolites 1 h after morphine or codeine are shown in Figure 1. In group M, morphine and its metabolites were detected in all the patients. In group C, morphine and/or its metabolites were not detected in 17 patients (36%). The mean (SD) plasma concentrations of morphine, M3G and M6G were 24.7 (10.1), 96.58 (40.5) and 29.3 (13) ng ml^{-1} respectively after morphine, and 4.5

(2.1), 44.8 (29) and 19.7 (16.5) ng ml^{-1} after codeine. There was a significant difference between the two treatment groups for the plasma concentrations of morphine and both glucuronide metabolites ($P<0.01$). There was no difference in M3G:M6G ratio, which was 4.2 (3.17) in group M and 3.8 (3.5) in group C ($P=0.6$).

Figure 2 shows the relationships of plasma morphine, M3G and M6G with phenotype for group C. Morphine concentrations were generally very low and could not be detected in an increasing proportion of patients with phenotypes associated with declining metabolic capacity. No morphine was found in the plasma of the two PMs (Fig. 2A). Plasma morphine concentrations were also related to phenotype, with a significant trend ($P<0.02$) across the groups (Fig. 2B). There was no difference in plasma morphine between the IM and IM/PM groups, but mean concentrations for both these groups were very low and close to the lower limit of measurement. Plasma concentrations of metabolites are shown in Figure 2C and D. The ratio of M3G:M6G was 4.5 (5.02) in the EM group and 3.4 (2.07) and 2.95 (2.39) in the IM and IM/PM groups respectively ($P>0.05$).

Comparisons of time to first analgesia were made using Kaplan–Meier survival curves 2 and 4 h after administration of either opioid (Fig. 3).[16] In the first 2 h, the number of patients who required extra analgesia was eight (16.7%) in group C and two (4.2%) in group M ($P<0.05$). By 4 h, 20 of the 48 (41.7%) patients in group C required extra analgesia compared with nine of the 48 (18.8%) patients in group M ($P<0.01$). No relationship could be established between the group C patients of each phenotype who needed rescue analgesia. PMs did not differ significantly from other

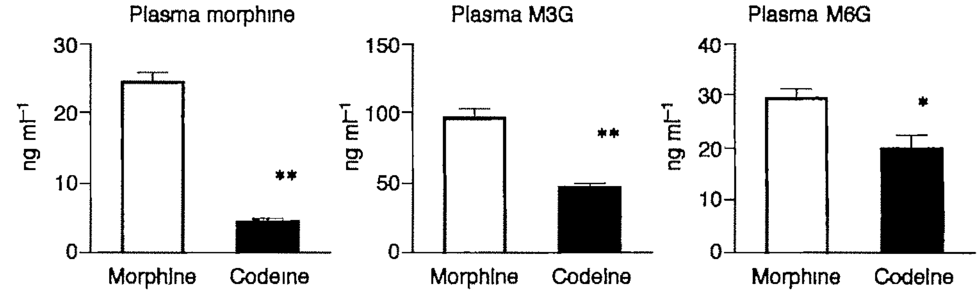


Fig 1 Plasma morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) concentrations in the morphine and codeine groups ($n=48$ for each group). Data are mean and SD $*P<0.01$; $**P<0.001$.

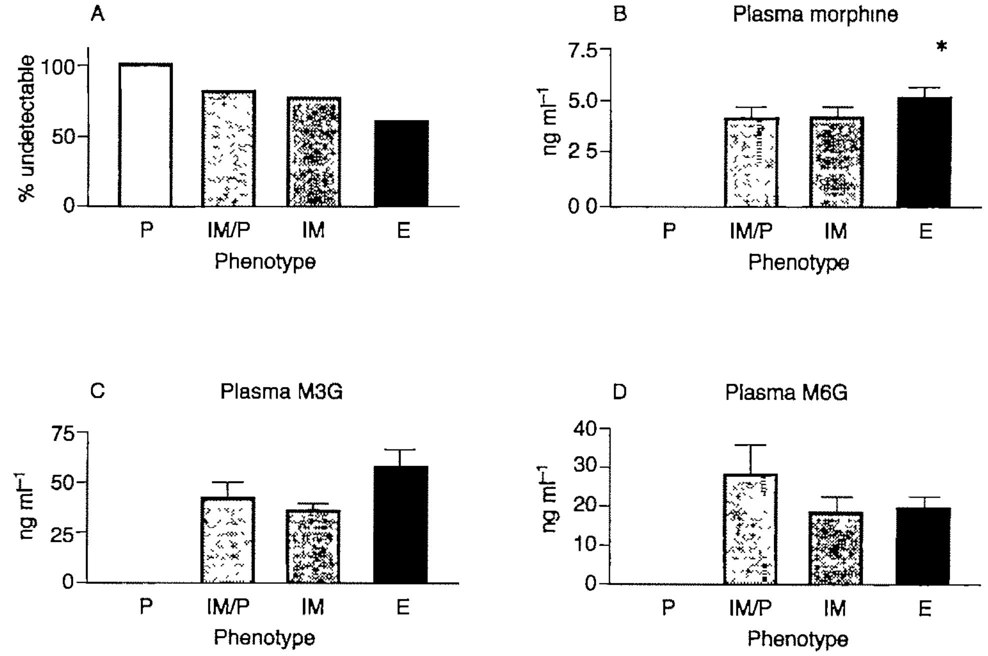


Fig 2 Relationship between plasma morphine, metabolites and phenotype for patients treated with codeine. P=poor metabolizers, IM/P=intermediate/poor metabolizers; E=extensive metabolizers. Data are mean and SD (A) Number of patients of each phenotype with undetectably low plasma morphine concentration. (B) Plasma morphine concentration in relation to phenotype $*P<0.02$ (C) Morphine-3-glucuronide (M3G) concentration in relation to phenotype. (D) Morphine-6-glucuronide (M6G) concentration in relation to phenotype.

phenotypes despite a demonstrated lack of plasma morphine. Overall, there was no relationship between plasma morphine, metabolite concentrations or M3G:M6G ratio and the requirement for extra analgesia.

Comparison of both behavioural and self-reporting pain scores, at rest and on swallowing, did not show a difference between groups C and M at any time point. Pain scores were generally higher on swallowing than at rest ($P<0.05$), with larger differences seen between pain on swallowing and at rest in group C compared with group M. Pain scores were also generally higher in recovery than at subsequent time points in children from both groups ($P<0.05$). Children in group C who received supplementary analgesia in the recovery room had higher pain scores at rest compared with the other children in group C ($P<0.05$). There was no difference in pain scores between the phenotypes in group C

The percentage of patients who vomited in the first 4 h after operation was 56.3 for group M and 29.2 for group C ($P<0.01$). Figure 4 shows a comparison between groups M and C for the number of patients who vomited in each time period. There was no difference between the two groups in the proportion of patients who vomited at <1, 1–2 and 4–8 h but the difference was significant at 2–4 h ($P<0.01$), with more vomiting in group M. In group C, neither of the PM patients vomited but otherwise postoperative nausea and vomiting was evenly distributed between the phenotypes ($P>0.05$). There was no difference between the two groups in the time to oral intake, which was measured from the end of surgery. Intravenous fluids were continued because of vomiting in two patients in group M and one in group C, but discharge from hospital was not delayed.

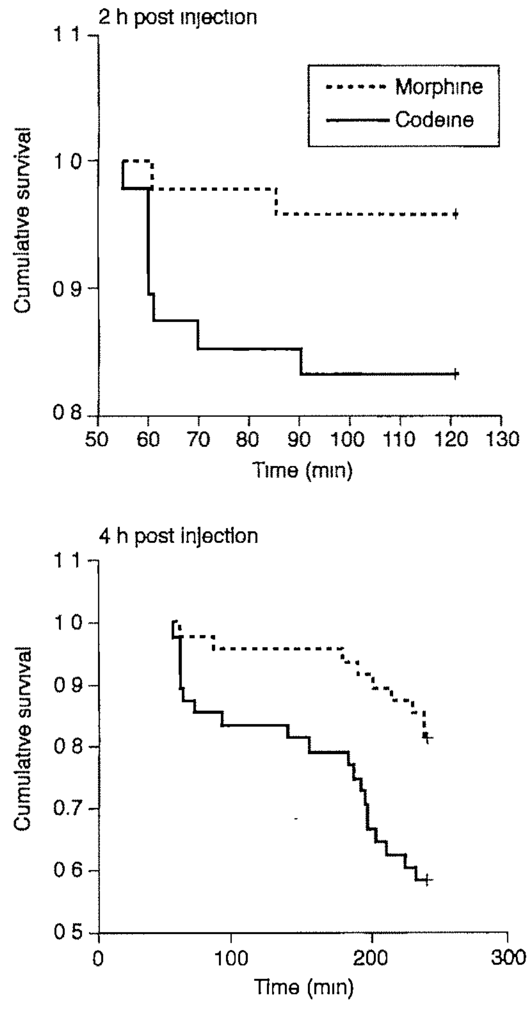


Fig 3 Time to first analgesia (Kaplan–Meier survival curves). $P<0\,05$ at 2 h, $P<0.01$ at 4 h

Figure 5 shows sedation scores at each of the time points for each group. Patients who received morphine were more sleepy at 2 h ($P<0.01$). By 4 h the degree of sedation was similar. There was no difference in respiratory rate between the two groups at any of the time points during the study

Five patients in the group C and none in group M required replacement of the laryngeal mask airway with a tracheal tube. On three occasions this was because of inability to maintain the airway on insertion of the surgical retractor, on one occasion it was because of an unsatisfactory airway in the anaesthetic room, and on the other occasion the tube was placed after an episode of laryngospasm. Pain scores on swallowing were not increased in this subgroup. One patient in each group had a prolonged stay in recovery (>1 h) because of slow awakening after anaesthesia. One patient in each group had postoperative bleeding that required a return to theatre some hours later. One morphine patient had significant swelling and pain the next day which delayed discharge, which in all other cases was the morning after the procedure.

Discussion

The mechanism of codeine analgesia is not completely understood but there is convincing evidence from both animal and human laboratory studies that it is wholly or substantially dependent on metabolism to morphine.[6 7 17 18] The activity of the enzyme complex responsible for this reaction is known to be genetically regulated, with a spectrum of phenotypes between normal or 'extensive' and

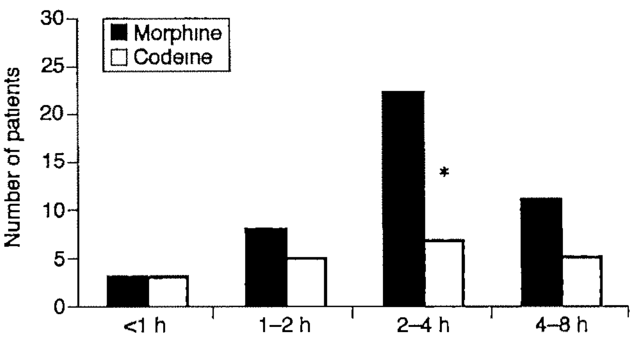


Fig 4 Postoperative vomiting *$P<0\,01$

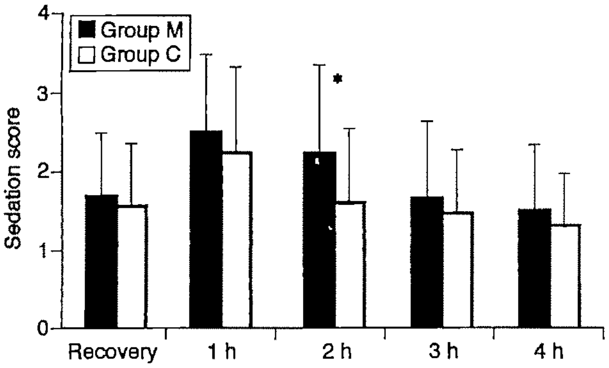


Fig 5 Postoperative sedation scores. M=morphine; C=codeine. *P<0 01.

absent or 'poor'. In this study we investigated the genotypes of a population of children who were having adenotonsillectomy and assigned them to phenotypes that should reflect this range of metabolic capability. A high proportion (46%) of the children studied had phenotypes associated with reduced activity of the enzyme. Plasma morphine and metabolite concentrations in children given the parent drug, codeine, were very low or absent in greater proportions of those in the low-activity groups, the actual values reflecting the range predicted by the phenotype.

Plasma morphine concentration has not been directly related to analgesia, but pharmacokinetic studies have suggested that a range of 5–65 ng ml^{-1} may be therapeutic in children.[19–21] One hour after administration of codeine in this study, mean plasma morphine was below this range in all phenotypes after codeine, including normal and extensive metabolizers. The half-life of both codeine and morphine after i.m. injection is 2–3 h, and the usual recommended dosing regimen for both is 4- to 6-hourly.[1, 22, 23] However, such low concentrations at 1 h imply that analgesia from codeine-derived morphine after that time would be unlikely.

In the second part of the present study, the analgesia and side-effects of codeine and morphine combined with diclofenac were compared. Diclofenac was included for ethical reasons because the concurrent use of opioid and NSAID (non-steroidal anti-inflammatory drug) analgesia is standard practice after adenotonsillectomy. Significantly more children needed rescue analgesia at 2 and 4 h in the group given codeine (group C) than in the group given morphine (group M). However, behavioural and self-report pain assessments did not differentiate between the groups at any stage of the study. All the mean scores were within the satisfactory range. However, the codeine subgroup who needed supplementary analgesia had significantly higher scores in recovery than the rest of that group. Although within group C plasma morphine was related to phenotype, no relationship could be found between phenotype and analgesia; as morphine concentrations were very low and differences in morphine production between phenotypes were small, this may not be surprising. The concurrent use of diclofenac may also have masked any differences between the groups, as such analgesic combinations are known to increase efficacy substantially in comparison with monotherapy (see below).

In the first 4 h after operation, 29.2% of the patients vomited in group C compared with 56.3% of patients in group M. Vomiting is common after adenotonsillectomy in children, with a reported incidence of between 30 and 75%.[24, 25] The causes are multiple and may include stimulation of laryngeal and pharyngeal reflexes, gastric irritation as a result of swallowed blood, anaesthetic agents and analgesic administration.[26, 27] Broadly, there was little difference between the two drug groups in terms of sedation and respiratory rate. Previous studies in both adults and children have suggested that, although the incidence of side-effects may be low, the overall efficacy of codeine is also low and analgesia may be inadequate for postoperative pain in some circumstances.[3, 28, 29] Indeed, in the adult some single-dose studies have shown no difference between codeine and placebo, and a quantitative systemic review suggests that codeine 60 mg has a number needed to treat (NNT) of 18, which is very high when compared with 5.0 for acetaminophen 600 mg and 3.1 for the combination.[30–32]

In conclusion, we have found that reduced ability to metabolize codeine to morphine was common in this population of children, and that plasma concentrations of morphine are generally very low 1 h after i.m. codeine for patients of all phenotypes, even those who have normal metabolic capability. Codeine analgesia with diclofenac was less reliable than morphine, but a clear relationship between plasma morphine or phenotype and analgesia could not be established. Uncertainties regarding the efficacy and any possible advantages of codeine over morphine or other opioids mean that its use cannot be recommended without reservation. Situations in which pain is known to be significant and pain assessment problematic present particular difficulties, which will only be heightened by the use of codeine.

Acknowledgements

DGW was supported by Simms Portex Ltd. The authors would like to thank Professor D J. Hatch and Dr C. Ferguson for their help in setting up this project, Dr J. de-Lima and Innes Kastner for processing the morphine samples and Dr M. Thomas and Ben Fletcher for the genetic analysis.

References

1 Dolhery C. *Therapeutic Drugs*, 2nd edn. Edinburgh: Churchill Livingstone, 1999; C317–20

2 Royal College of Paediatrics and Child Health. *Prevention and Control of Pain in Children*, 1st edn. London: BMJ Publishing Group, 1997

3 Semple D, Russel S, Doyle E, Aldridge LM. Comparison of morphine sulphate and codeine phosphate in children undergoing adenotonsillectomy. *Paediatr Anaesth* 1999; **9**: 135–8

4 Stoneham MD, Walters FJM. Post-operative analgesia for

craniotomy patients: current attitudes among neuroanaesthetists. *Eur J Anaesthesiol* 1995; **12**: 571–5

5 Hatch DJ, Sumner E. Neonatal anaesthesia—basic principles. In: *The Surgical Neonate: Anaesthesia and Intensive Care*. London: Edward Arnold, 1995; 142

6 Williams DG, Hatch DJ, Howard RF. Codeine phosphate in paediatric medicine. *Br J Anaesth* 2001; **86**: 413–21

7 Sindrup SH, Brosen K. The pharmacogenetics of codeine hypoalgesia. *Pharmacogenetics* 1995, **5**: 335–46

8 Daly AK, Brockmoller J, Broly, *et al.* Nomenclature for human CYP2D6 alleles. *Pharmacogenetics* 1996; **6**: 193–202

9 Marez D, Legrand M, Sabbagh N, *et al.* Polymorphism of the cytochrome P450 CYP2D6 gene in a European population: characterization of 48 mutations and 53 alleles, their frequencies and evolution. *Pharmacogenetics* 1997; **7**· 193–202

10 Sindrup SH, Brosen K, Bjerring P, *et al.* Codeine increases pain thresholds to copper vapor laser stimuli in extensive but not poor metabolizers of sparteine. *Clin Pharmacol Ther* 1990; **48**: 686–93

11 Rogers JF, Findlay JWA, Hull JH, *et al* Codeine disposition in smokers and nonsmokers. *Clin Pharmacol Ther* 1982; **32**: 227

12 Online Mendelian Inheritance In Man. Cytochrome P450, subfamily IID; CYP2D. Online Mendelian Inheritance In Man 1999 (id:124030)

13 Sachse C, Brockmoller J, Hilderbard M, Muller K, Roots I. Correctness of prediction of the CYP2D6 phenotype by genotyping 47 intermediate and poor metabolisers of debrisoquine. *Pharmacogenetics* 1998; **8**: 181–5

14 Wong D, Whaley L. *Clinical Handbook of Pediatric Nursing*, 2nd edn. St Louis: C.V. Mosby, 1986; 373

15 McGrath PJ, Johnson G, Goodman JT, Schillinger J, Dunn J, Chapman J CHEOPS: A behavioural scale for rating postoperative pain in children. In: *Advances in Pain Research and Therapy*, volume 9. New York: Raven Press, 1985; 395–401

16 Altman DG, Bland JM Time to event (survival) data. *Br Med J* 1998; **317**: 468–9

17 Cleary J, Mikus G, Somogyi AA, Bochner F. The influence of pharmacogenetics on opioid analgesia: studies with codeine and oxycodone in the Sprague–Dawley/Dark Agouti rat model. *J Pharmacol Exp Ther* 1994; **271**: 1528–34

18 Eckhardt K, Li S, Ammon S, Schanzle G, Mikus G, Eichelbaum M. Same incidence of adverse drug events after codeine administration irrespective of the genetically determined differences in morphine formation. *Pain* 1998; **76**· 27–33

19 Dhalstrom B, Bolme P, Feychting H, Noack G, Paalzow L. Morphine kinetics in children. *Clin Pharmacol Ther* 1979; **26** 354–65

20 Lynn AM, Slattery JT. Morphine pharmacokinetics in early infancy. *Anesthesiology* 1987; **66**: 136–9

21 Olkkola KT, Maunuksela EL, Korpela R, Rosenberg PH. Kinetics and dynamics of postoperative intravenous morphine in children *Clin Pharmacol Ther* 1988; **44**: 128–36

22 Kart T, Christrup LL, Rasmussen M. Recommended use of morphine in neonates, infants and children based on a literature review. Part 1. Pharmacokinetics. *Paediatr Anaesth* 1997; **7**: 5–11

23 British Medical Association and Royal Pharmaceutical Society of Great Britain. *British National Formulary*, 40th edn. London: British Medical Association and Royal Pharmaceutical Society of Great Britain, 2000

24 Gunter JB, Varughese AM, Harrington JF, *et al.* Recovery and complications after tonsillectomy in children: a comparison of ketorolac and morphine. *Anesth Analg* 1995; **81**: 1136–41

25 Kermode J, Walker S, Webb I. Postoperative vomiting in children. *Anaesth Intensive Care* 1995, **23**: 196–9

26 Ved SA, Walden TL, Montana J. Vomiting and recovery after outpatient tonsillectomy and adenoidectomy in children: comparison of four anesthetic techniques using nitrous oxide with halothane or propofol. *Anesthesiology* 1996, **85**. 4–10

27 Rose JB, Watcha MF Postoperative nausea and vomiting in paediatric patients. *Br J Anaesth* 1999; **83**· 104–17

28 McEwan A, Andrews KA, Sigston PE, *et al.* A comparison of rectal and intramuscular codeine phosphate in children following neurosurgery. *Paediatr Anaesth* 2000; **10**· 189–93

29 Quiding H, Lundqvist G, Boreus LO, Bondesson U, Ohrvik J. Analgesic effect and plasma concentrations of codeine and morphine after two dose levels of codeine following oral surgery. *Eur J Clin Pharmacol* 1993; **44**: 319–23

30 Jochimsen PR, Noyes R. Appraisal of codeine as an analgesic in older patients. *J Am Geriatr Soc* 1978; **26**: 521–3

31 Hoing S, Murray KA. An appraisal of codeine as an analgesic single-dose analysis. *J Clin Pharmacol* 1984; **24**· 96–102

32 Moore A, Collins S, Carroll D, McQuay H. Paracetamol with and without codeine in acute pain: a quantitative systematic review *Pain* 1997, **70**: 193–201

British Journal of Anaesthesia 89 (6): 846–8 (2002)

Plasma lidocaine concentrations following insertion of 2% lidocaine gel into the uterine cavity after uterine balloon thermal ablation

G. F. Rousseau[1]*, M. Oram[2], J. Barrington[3], M. Priston[4] and M. Swart[2]

[1]Department of Anaesthesia, North Devon District Hospital, Barnstaple EX31 4JB, UK. [2]Department of Anaesthesia and Intensive Care and [3]Department of Obstetrics and Gynaecology, Torbay Hospital, Torquay TQ2 7AA, UK. [4]Pharmacy Department, Derriford Hospital, Plymouth PL6 8DH, UK

**Corresponding author. E-mail: guy.rousseau@virgin.net*

Background. Uterine balloon thermal ablation is used to treat menorrhagia. We thought that intrauterine application of 2% lidocaine gel could reduce postoperative pain after this procedure. Before using this technique we wished to establish how much lidocaine is absorbed systemically from the uterine cavity after thermal ablation.

Methods. Ten ASA I–II patients (age 38–50 yr) underwent uterine balloon thermal ablation under general anaesthesia. They each had 11 ml of 2% lidocaine gel (Instillagel™) inserted into the uterine cavity at the end of the procedure. Blood samples were taken at 5, 15, 30 and 60 min after insertion and lidocaine concentrations were measured using high-performance liquid chromatography.

Results. Mean (range) plasma lidocaine concentrations at 5, 15, 30 and 60 min were 40.3 (0–221.9), 66.3 (0–271.9), 64.9 (0–208) and 75 (0–212) ng ml^{-1}, respectively.

Conclusion. There was minimal systemic absorption of lidocaine from the uterus following uterine balloon thermal ablation. Measured concentrations were well below the toxic plasma concentration for lidocaine (8–10 μg ml^{-1}).

Br J Anaesth 2002; **89**: 846–8

Keywords: anaesthetics local, lidocaine; uterus, thermal ablation

Accepted for publication: June 17, 2002

Uterine balloon thermal ablation (Thermochoice Gynecare) is a new method for treating menorrhagia.[1 2] The technique involves inserting a balloon-tipped catheter through the dilated cervix and inflating the balloon with 5% dextrose solution. The balloon, which is now in contact with the walls of the uterine cavity, is heated to 87°C for 8 min. This results in a thermal ablation of the endometrium and adjacent myometrium to a depth of up to 15 mm.[3] A number of different anaesthetic techniques have been used for the procedure, ranging from local anaesthetic blocks under sedation, to regional and general anaesthesia. Intrauterine administration of 2% lidocaine gel (Instillagel™) may be a simple method for reducing postoperative pain. We were concerned that there may be greater systemic absorption of lidocaine when it is applied to tissues that have just had a thermal injury compared with lidocaine gel applied to undamaged tissues. Before using intrauterine lidocaine gel for analgesia, we wanted to assess how much systemic absorption of lidocaine occurs when lidocaine gel is applied to the uterine cavity after balloon thermal ablation.

Methods

The local Research and Ethics Committee approved the study and informed written consent was obtained. Ten patients over 18 yr of age who were undergoing uterine balloon thermal ablation were entered into the study. Patients who were allergic to the study drugs, had a history of epilepsy or liver disease, or who were unable to give consent were excluded from the study. A Clinical Trials Exemption Certificate was obtained from the UK Medicines Control Agency. Before surgery, patients were given diclofenac 100 mg, metoclopramide 10 mg and acetaminophen 1 g orally. Oxygen was administered via a Hudson mask at 4 litre min^{-1}. Fentanyl 100 μg i.v. was given for analgesia and ondansetron 4 mg i.v. as a prophylactic

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

antiemetic. Anaesthesia was induced and maintained by an infusion of 1% propofol with alfentanyl 20 μg ml^{-1}.

In the postoperative recovery area, patients received additional fentanyl 50 μg i.v. until comfortable. Tylex™ (acetaminophen 500 mg and codeine phosphate 30 mg), two tablets every 6 h, and diclofenac 50 mg orally every 8 h were given as required for further analgesia.

After induction of anaesthesia, a 14-gauge i.v. cannula was placed in the antecubital fossa for postoperative blood sampling. The cervix was dilated with a size-5 Hagar dilator and the depth of the uterine cavity measured with a uterine sound. The balloon-tipped catheter was inserted into the uterine cavity up to this depth. The balloon was inflated with 5% dextrose 5–15 ml until a pressure of 160–180 mm Hg was reached. The dextrose solution was then heated to 87°C for 8 min. To maintain contact with the endometrium, the pressure in the balloon was kept at 160–180 mm Hg. At the end of the procedure, 2% lidocaine 11 ml was inserted into the uterus using an introducer (Instillaquil). Blood samples were taken at 5, 15, 30 and 60 min after insertion of the lidocaine gel. The plasma was separated using 4-ml Vacuette tubes (Greiner Turbotechnik) within 3 h and stored at −20°C. Plasma lidocaine concentration was measured using high-performance liquid chromatography and the values expressed in ng ml^{-1} plasma.[4] The extraction method was shown to be accurate and precise over the concentration range investigated: the intraday precision coefficients of variation and relative error were, respectively, 6.70% and 2.90% at 50 ng ml^{-1}, 5.14% and 3.50% at 100 ng ml^{-1} and 3.88% and 9.03% at 200 ng ml^{-1}. Interday precision coefficients of variation and relative error were, respectively, 6.47% and 0.12% at 50 ng ml^{-1}, 3.84% and 2.14% at 100 ng ml^{-1} and 2.80% and 2.19% at 200 ng ml^{-1}.

Table 1 Patient characteristics and peak plasma lidocaine concentrations

Patient	Age (yr)	Weight (kg)	Height (m)	Peak plasma lidocaine concentration (ng ml^{-1})	Time to peak (min)
1	42	50.8	1.58	37.9	60
2	54	105	1.65	16.3	60
3	45	70.0	1.60	272	15
4	38	71.2	1.64	71.1	60
5	47	110	1.63	33.7	60
6	50	85.0	1.62	20.8	60
7	41	57.0	1.61	104	15
8	49	55.0	1.58	72.8	15
9	47	62.6	1.60	190	60
10	45	79.8	1.66	0	60

Results

Patient characteristics and peak plasma concentrations of lidocaine are shown in Table 1. The maximum plasma concentration measured was 272 ng ml^{-1}, which is below the toxic concentration. Plasma lidocaine concentrations measured at 5, 15, 30 and 60 min after application of intrauterine lidocaine for each subject are shown in Figure 1.This indicates that the plasma lidocaine concentration had peaked or reached a plateau. There were no clinical symptoms or signs of local anaesthetic toxicity.

Discussion

We found that plasma lidocaine concentrations after the insertion of lidocaine gel 220 mg into the uterine cavity after uterine balloon thermal ablation were well below those reported to cause symptoms and signs of toxicity. The highest concentration recorded was 272 ng ml^{-1} at 15 min after insertion. In a study by Folds and colleagues,[5] volunteers began to experience symptoms and display signs of lidocaine toxicity at a mean plasma concentration of 8–10 μg ml^{-1}, which is tenfold higher than our highest recorded level. Our results demonstrate no early peak at 5 min, which could have occurred from direct intravascular

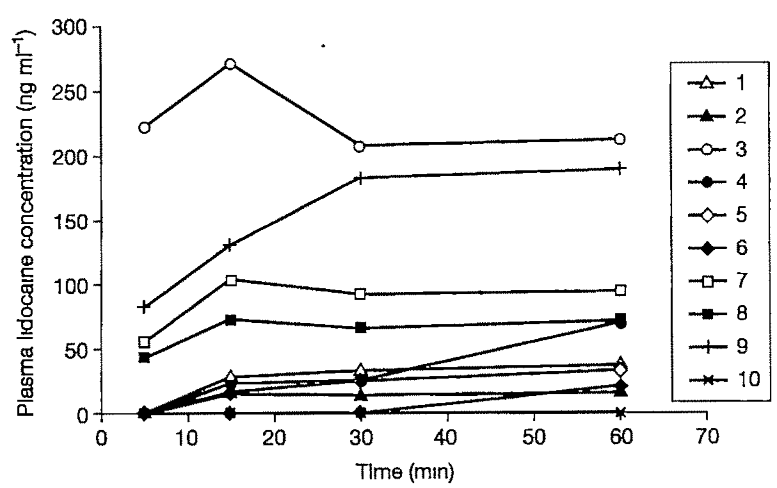


Fig 1 Plasma lidocaine concentrations in individual patients at 5, 15, 30 and 60 min after intrauterine insertion of 2% lidocaine gel 11 ml

administration. Peak concentrations were recorded at 15 and 60 min, indicating that concentrations are either still rising at 15 min or reaching a plateau, making the likelihood of an early missed peak unlikely. If there were to be an early peak plasma concentration before 5 min, the neurological symptoms and signs may go unrecognized as patients would still be under the effect of general anaesthesia, which would both mask the symptoms and protect the patient by raising the seizure threshold.

We chose to use lidocaine in a gel because it is available in this form. In addition, it is supplied in a syringe that is incompatible with i.v. needles and cannulae, which reduces the risk of inadvertent i.v. injection. The dose of lidocaine was not adjusted for weight or body mass index (BMI) because we wanted to evaluate a simple one-dose regimen for adults. Other factors may affect how much lidocaine is absorbed, such as uterine cavity size and uterine muscle spasm, both of which will alter the volume of lidocaine that remains in the uterine cavity. Peak plasma concentrations in those with a lower body weight or BMI were below toxic concentrations.

In conclusion, the amount of lidocaine absorbed systemically after 11 ml of 2% lidocaine gel is placed in the uterine cavity following intrauterine balloon thermal ablation is low. Further studies are needed to evaluate the analgesic effects of intrauterine lidocaine gel after balloon thermal ablation.

Acknowledgements

This study was supported by a grant from the Torbay Special Medical Projects and Research Fund.

References

1 Meyer WR, Walsh BW, Grainger DA, *et al.* Thermal balloon and rollerball ablation to treat menorrhagia: a multicenter comparison. *Obstet Gynecol* 1998; **92**: 98–103

2 Amso NN, Stabinsky SA, McFaul P, *et al.* Uterine thermal balloon therapy for the treatment of menorrhagia: the first 300 patients from a multi-centre trial. *Br J Obstet Gynaecol* 1998; **105**: 517–23

3 Anderson LF, Meinert L, Rygaard C, *et al.* Thermal balloon endometrial ablation: safety aspects evaluated by serosal temperature, light microscopy and electron microscopy. *Eur J Obstet Gynecol Reprod Biol* 1998; **79**: 63–8

4 Zivanovic L, Agatonovic-Kustrin S, Vasiljevic M, Nemcova I. Comparison of high-performance and thin-layer chomatographic methods for the assay of lidocaine. *J Pharm Biomed Anal* 1996; **14**: 1229–32

5 Foldes FF, Malloy R, McNall PG, Koukal LR. Comparison of toxicity of intravenously given local anaesthetic agents in man. *JAMA* 1960; **172**: 1493–8

British Journal of Anaesthesia **89** (6) 849–52 (2002)

Effects of intramuscular administration of lidocaine or bupivacaine on induction and maintenance doses of propofol evaluated by bispectral index

M. Senturk*, K. Pembeci, F. Menda, T. Ozkan, B. Gucyetmez, M. Tugrul, E. Camci and K. Akpir

Department of Anaesthesiology, Istanbul University, Istanbul Medical Faculty, Capa 34390, Istanbul, Turkey

**Corresponding author. E-mail: merthasta@yahoo.com*

Background. Interest in combining local and general anaesthesia has lead to studies investigating possible interactions. In a prospective, randomized, double-blind study, we tested whether local anaesthetics administered i.m. potentiate the hypnotic effect of propofol.

Methods. Sixty patients (three groups, n=20) undergoing lower abdominal surgery with total i.v. propofol anaesthesia were investigated. Patients in Group B received i.m. bupivacaine (5 mg ml^{-1}) 1 mg kg^{-1}, patients in Group L received i.m. lidocaine (100 mg ml^{-1}) 2 mg kg^{-1} and patients in Group C received i.m. saline 5 ml before operation. Hypnosis was measured with bispectral index (BIS).

Results. The induction (BIS <45), and the maintenance doses of propofol (BIS between 40 and 50) were significantly less in Group B and Group L compared with the control group. Induction doses were 1.58 (SD 0.39), 1.56 (0.24) and 2.03 (0.33) mg kg^{-1} respectively; P<0.0001. Maintenance doses were 6.33 (2.06), 7.08 (1.23) and 9.95 (2.02) mg kg^{-1} respectively in the first hour; P<0.0001. Groups B and L were associated with an attenuated haemodynamic response to both induction and intubation.

Conclusion. I.M. administered local anaesthetics are associated with a decrease in both the induction and maintenance doses of propofol during total i.v. anaesthesia and a reduction in haemodynamic responses.

Br J Anaesth 2002; **89**: 849–52

Keywords: anaesthetic techniques, i.v.; anaesthetics local; monitoring, bispectral index

Accepted for publication: July 8, 2002

The growing interest in combining local and general anaesthesia has led to studies investigating possible interactions between general anaesthetics and local anaesthetics administered via either spinal,[1] epidural,[2 3] i.v.[4] or i.m.[5 6] route.

In previous studies it has been shown that i.m. administration of either lidocaine or bupivacaine enhances the hypnotic effects of i.v. thiopental[5] and propofol.[6] However, these studies only concluded that local anaesthetics administered i.m. can reduce the induction dose of i.v. general anaesthetics, no evaluation of the effect of systemically used local anaesthetics on the maintenance dose of the general anaesthetic was carried out. Additionally, the results of both studies were based on responses to verbal commands. More reliable results can be obtained using bispectral index (BIS), which has been shown to be a specific and sensitive monitor of the hypnotic component of anaesthesia.[7] In a prospective, randomized, double-blind study, we investigated whether lidocaine or bupivacaine administered i.m. reduces the induction and the maintenance dose of propofol during BIS-guided total i.v. anaesthesia (TIVA).

Methods

With informed patient consent and approval from the ethical committee of the faculty, we studied 60 patients, aged 20–50 yr, ASA I or II, weighing 50–80 kg, undergoing minor elective lower abdominal surgery expected to last ≥1 h. To detect a decrease of 0.35 mg kg^{-1} of the induction dose of propofol (accepting an alpha error of 5% and a beta

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Table 1 Patient characteristics, mean (SD) [range] No significant differences

	Group B (*n*=20)	**Group L** (*n*=20)	**Group C** (*n*=20)
Gender (F/M)	7/13	8/12	6/14
Age (yr)	37.6 [21–50]	38.5 [23–49]	37.6 [20–48]
Weight (kg)	67.8 (7.8)	67.6 (6.3)	65.5 (7.7)

error of 10%), the required study size was 16 patients per group. Patients taking cardiovascular medication, with known hypersensitivity to local anaesthetics, neurological disorders, hypertension, baseline systolic arterial pressure (SAP) <100 mm Hg, heart rate (HR) <55 beat min^{-1}, or any serious medical conditions that would interfere with cardiovascular response assessment were excluded.

Patients did not receive premedication. They were prehydrated with NaCl 0.9% 500 ml solution, and were connected to an electrocardiograph monitor, automatic arterial pressure cuff and a pulse oximeter (Horizon 2000, Mennen Medical, Rehovot, Israel). BIS was monitored using a BIS sensor (Aspect Medical Systems, Natick, MA, USA) applied to the forehead as described by the manufacturer (BIS monitor Model A-2000™, Aspect Medical Systems, Natick, MA, USA). Patients were then allocated randomly to one of three groups according to a sealed envelope technique in a double-blind manner. In Group B, 20 patients received i.m. bupivacaine (5 mg ml^{-1}) 1 mg kg^{-1} (Marcaine 0.5% flk AstraZeneca İlaç AŞ, Istanbul, Turkey), administered into the gluteus muscle 30 min before induction of anaesthesia. In Group L, 20 patients received i.m. lidocaine (100 mg ml^{-1}) 2 mg kg^{-1} (Aritmal 10% ampul, Biosel İlaç AŞ, Istanbul, Turkey), administered into the gluteus muscle 10 min before induction of anaesthesia. In Group C, 20 patients served as controls and received i.m. saline 5 ml into the gluteus muscle 10 min before induction of anaesthesia. All i.m. injections were performed by an independent practitioner. HR, mean arterial pressure (MAP) and BIS values were recorded at t_0 (before i.m. administration), t_1 (before induction of anaesthesia), t_2 (after induction of anaesthesia) and t_3 (after intubation).

After a bolus dose of fentanyl 1.5 μg kg^{-1} i.v., a physician, who was blinded to the dose or type of local anaesthetic (or saline) administered earlier, injected propofol 10 mg (1 ml) in 5 s every 15 s until the BIS score fell below 45. The total dose of propofol required to achieve a BIS below 45 was recorded in mg kg^{-1}. When BIS <45, response to verbal commands was evaluated. Tracheal intubation was accomplished after administration of rocuronium 0.6 mg kg^{-1}. Volume controlled ventilation (Dräger SA2, Drägerwerk, Lübeck, Germany) was started with 10 ml kg^{-1} tidal volume and ventilatory frequency was adjusted to maintain endtidal carbon dioxide tension 30–35 mm Hg. Lungs were ventilated with 50% oxygen, 50% air.

After intubation, infusion of propofol 10 mg kg^{-1} h^{-1} and remifentanil 0.25 μg kg^{-1} min^{-1} were started. The dose of propofol was titrated to keep the BIS score between 40 and 50. When the BIS score was out of these limits for ≥10 s the dose of propofol was changed by 1 mg kg^{-1} h^{-1} every 20 s. The total maintenance dose of propofol during the first hour of anaesthesia was recorded in mg kg^{-1} h^{-1}.

Inadequate analgesia was defined as response to surgical stimuli by hypertension (SAP >20% above preoperative baseline value for >5 min) or tachycardia (HR >20% above preoperative baseline value), while BIS level was between 40 and 50. In cases of inadequate analgesia, patients were given bolus doses of remifentanil 0.5 μg kg^{-1}. If this treatment was unsuccessful, the remifentanil infusion rate was doubled.

Bradycardia was defined as HR <40 beat min^{-1} and hypotension as a decrease in SAP >20% of the baseline value. Hypotension was treated by infusion of lactated Ringer's solution 3–5 ml kg^{-1}, and if necessary, with ephedrine 5 mg i.v. Bradycardia was treated with atropine 0.5 mg i.v. The frequency of hypotension, bradycardia and inadequate analgesia and supplemental remifentanil doses was recorded.

To assess intraoperative awareness, a number was repetitively recited to each patient four times during anaesthesia at 5, 10, 15 and 20 min. The patients were specifically questioned for recall of this number.

Analysis of variance (ANOVA) was used to evaluate the differences in patient characteristics, HR, MAP, BIS-values, and propofol doses for induction and maintenance between the groups. Data at different times within the groups were compared with a repeated measures ANOVA (GraphPad InStat™, GraphPad Software V2.02). The alterations in HR and MAP after the induction and intubation were also compared in the three groups. To compare the frequency of hypotension, bradycardia and inadequate analgesia, an appropriate χ^2-test was used. $P<0.05$ was regarded as statistically significant.

Results

There were no statistically significant differences with respect to patient characteristics between the groups (Table 1). Propofol doses required for the induction of anaesthesia were significantly less in patients in Groups B and L compared with the control group ($P<0.0001$; 1.58 (0.39), 1.56 (0.24) and 2.03 (0.33) mg kg^{-1}, respectively; $P<0.01$ between Groups B and C, and between Groups L and C, Fig. 1). The maintenance doses for the first hour of surgery were also significantly less in these patients ($P<0.0001$; 6.33 (2.06), 7.08 (1.23) and 9.95 (2.02) mg kg^{-1} h^{-1} respectively; $P<0.01$ between Groups B and C, and between Groups L and C, Fig. 2). There was no statistical difference between Groups B and L regarding the induction and maintenance doses of propofol.

HR and MAP values are shown in Tables 2 and 3. HR was decreased after induction by 13.7 (6.2), 14.0 (5.8), 14.5 (4.6)% in patients receiving bupivacaine, lidocaine and

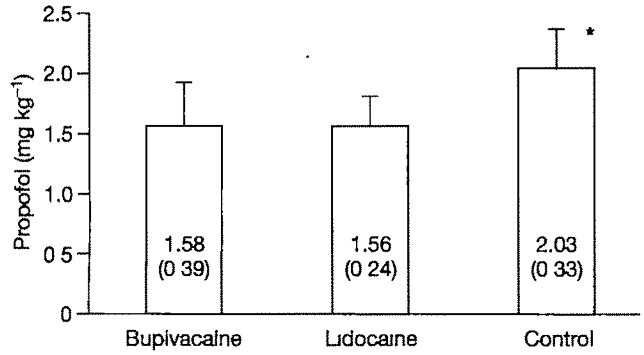


Fig 1 Propofol requirement to achieve BIS <45 during induction. Administration of i.m. bupivacaine and lidocaine resulted in a significant decrease. Values inside bars show mean (SD) doses. (*P<0.001 between bupivacaine and control, and between lidocaine and control.)

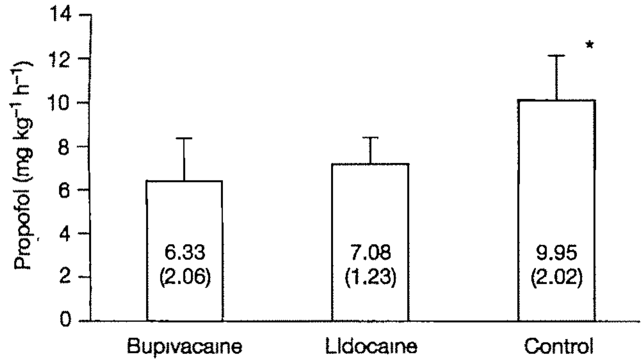


Fig 2 Propofol requirement to maintain BIS between 40 and 50 during maintenance of anaesthesia. Administration of i.m. bupivacaine and lidocaine resulted in a significant decrease. Values inside bars show mean (SD) doses. (*P<0.001 between bupivacaine and control, and between lidocaine and control.)

saline, respectively (no statistically significant differences). The increase in HR after intubation was statistically different between the groups (P=0.0003; 11.8 (7.9), 16.1 (9.9) and 25.5 (12.3)% in Groups B, L and C, respectively; P<0.001 between Groups B and C, P<0.05 between Groups L and C).

Regarding the MAP, the decrease after induction and increase after intubation were both significantly less in patients receiving bupivacaine compared with Groups L and C. Decrease after induction: P<0.0001; 20.3 (7.3), 28.5 (5.5) and 28.8 (7.1)% in Groups B, L, and C respectively; P<0.001 between Groups B and L, and between Groups B and C. Increase after intubation: P<0.0001; 12.4 (7.2), 26.8 (10.9), 31.8 (10.4) in Groups B, L, and C, respectively; P<0.001 between Groups B and L, and between Groups B and C.

There were no differences between the BIS values before and after the injection (t_0 and t_1) of local anaesthetic/saline [95.1 (1.7) at t_0 and 95.4 (0.8) at t_1, P>0.05]. The difference between t_2 and t_3 was also not significant [43.2 (0.8) at t_2 and 44.1 (2.0) at t_3, P>0.05].

Table 2 Heart rate, mean (SD) NB P<0.001 between t_1–t_2 and t_2–t_3

	Group B (beat min^{-1})	Group L (beat min^{-1})	Group C (beat min^{-1})
t_0	85.7 (15.3)	84.9 (11.7)	83 (13.1)
t_1	85.3 (15.4)	86.4 (14.7)	85 (16.7)
t_2	73.7 (14.4)	74.1 (12.1)	72.5 (14.3)
t_3	82.5 (15.3)	85.3 (10.9)	89.9 (12.5)

Table 3 Mean arterial pressure, mean (SD). NB P<0.001 between t_1–t_2 and t_2–t_3

	Group B (mm Hg)	Group L (mm Hg)	Group C (mm Hg)
t_0	100.1 (7.8)	103.8 (9.5)	105.9 (14.1)
t_1	102.1 (9.4)	104.9 (13.3)	101.3 (10.5)
t_2	81.1 (7.7)	75.1 (11.6)	71.7 (6.4)
t_3	91 (8.9)	94.3 (10.5)	94.2 (8.1)

At the end of the induction period, no response to verbal commands was observed (BIS <45). Awareness or inadequate analgesia was observed in no patients. Except for the hypotension in two patients in each group, haemodynamic complications were not seen. No signs of local anaesthetic toxicity or side-effects were observed in any patient.

Discussion

Our study showed that i.m. administration of local anaesthetics lead to a reduction in both the induction and maintenance doses of propofol to maintain the same BIS value.

The interaction of local and general anaesthetics has been investigated in several studies. Hodgson and colleagues[2] suggested three mechanisms for the reduction of MAC of volatile anaesthetic agents when combined with epidural anaesthesia: (i) systemic general anaesthetic effects of absorbed epidural lidocaine; (ii) direct epidural sensory block of the noxious stimulus and (iii) subanaesthetic concentrations of epidural lidocaine depressing spinal cord motor function. They concluded that the MAC-sparing effect of epidural anaesthesia in combination with general anaesthesia is most likely caused by central effects of spinal deafferentation, not to the systemic effects of lidocaine nor to direct neural block of spinal nerves. Our results do not support this conclusion. In another study it has been shown that i.v. lidocaine infusion has a MAC-sparing effect of 10–28%.[4] In our study, an i.v. anaesthetic has been used instead of inhalational anaesthetics, and lidocaine was administered via the i.m. route. It can be concluded that systemic general anaesthetic effects of absorbed local anaesthetics play an important role in the reduction of the dose of the general anaesthetic.

The effects of i.m. administration of lidocaine and bupivacaine on the induction doses of thiopental and propofol have been described.[5 6] The results of these studies and the present study are similar. However, there are two important differences. Firstly, in our study, not only the induction, but also the maintenance doses of propofol were investigated. Secondly, in these studies the effects of local anaesthetics on the general anaesthetic effect of i.v. anaesthetics were shown and compared only by the responses to verbal commands and not by BIS. In our study, both the loss of response to commands and BIS were used.

According to several studies, there are two main mechanisms that may explain the interaction of local and general anaesthetics. Firstly, most local anaesthetics bind to sodium channels in the inactivated state, preventing subsequent channel activation and the large transient sodium influx associated with membrane depolarization.[9] General anaesthetics are known to have some effects on the central nervous system, which are not unlike those of local anaesthetics. Both volatile anaesthetics and barbiturates have been shown to block sodium channels and thus prevent action potential formation in central neurones. Immobilization of the gating charge caused by the general anaesthetics has also been implicated in local anaesthetic action. Studies show that general anaesthetics do indeed increase the proportion of channels in the closed inactive state.[10–12]

Secondly, it is well known that propofol enhances GABAergic currents, which facilitate inhibitory neurotransmission in neurones.[13] Most i.v. anaesthetics inhibit the specific GABA uptake process *in vitro* in striatal nerve terminals, some, such as propofol, at clinically relevant concentrations.[14] It has been shown that local anaesthetics also potentiate GABA-mediated Cl^- currents by inhibiting GABA uptake.[15] These common mechanisms of action of local and general anaesthetics may explain how the hypnotic effect of i.v. propofol is enhanced by i.m. administration of bupivacaine or lidocaine.

We did not observe any signs of local anaesthetic toxicity or side-effects. The highest doses of local anaesthetics administered in our study were less than half the recommended maximum clinical doses[16] and were similar to doses administered in previous studies.[5] [6] Further studies are necessary to evaluate the effects of different doses of both lidocaine and bupivacaine on the doses of general anaesthetics after i.m. administration. We administered i.m. lidocaine 10 min and i.m. bupivacaine 30 min before i.v. administration of propofol because, at these times, blood concentrations reach a peak.[16]

Changes in haemodynamic values were not the primary variable in our study. The attenuation of the cardiovascular response to intubation after i.v. lidocaine has been recognized for some time. However, there are few studies examining the effects of i.m. administration. Bupivacaine was associated with a more stable haemodynamic status after both induction and intubation compared with control and lidocaine. Similarly, both lidocaine and bupivacaine were associated with a reduced increase in heart rate after intubation. Whether these were caused by the reduction in propofol doses, or by the direct effect of the i.m.-administered local anaesthetics is unclear.

Acknowledgements

This work was supported by the Research Fund of The University of Istanbul (Project number. 1725/15082001).

References

1 Tverskoy M, Shagal M, Finger J, Kissin I. Subarachnoid bupivacaine blockade decreases midazolam and thiopental hypnotic requirements. *J Clin Anesth* 1994; **6**: 487–90

2 Hodgson P, Liu S, Gras T. Does epidural anesthesia have general anesthetic effects? *Anesthesiology* 1999; **91**: 1687–92

3 Tverskoy M, Shifrin V, Finger J, Fleyshman G, Kissin I. Effect of epidural bupivacaine block on midazolam requirements. *Reg Anesth* 1996; **21**: 209–13

4 Himes RS, DiFazio CA, Burney RG. Effects of lidocaine on the anesthetic requirements for nitrous oxide and halothane. *Anesthesiology* 1977; **47**: 437–40

5 Tverskoy M, Ben Shlomo I, Vainshtein M, Zohar S, Fleyshman G. Hypnotic effect of i.v. thiopentone is enhanced by i.m. administration of either lignocaine or bupivacaine. *Br J Anaesth* 1997; **79**: 798–800

6 Ben Shlomo I, Tverskoy M, Fleyshman G, Chernlavsky G. Hypnotic effect of i.v. propofol is enhanced by i.m. administration of either lignocaine or bupivacaine. *Br J Anaesth* 1997; **78**: 375–7

7 Rosow C, Manberg PJ. Bispectral index monitoring. *Anesthesiol Clin North America* 2001; **19**: 947–66

8 Drummund JC. Monitoring depth of anesthesia: with emphasis on the application of the bispectral index and the middle latency auditory evoked response to the prevention of recall. *Anesthesiology* 2000; **93**: 876–82

9 Morgan GE Jr, Mikhail MS. Local anesthetics. In: *Clinical Anesthesiology*, 2nd Edn. Stamford, Connecticut: Appleton & Lange, 1996; 193–200

10 Kendig JJ, Courtney KR, Cohen EN. Anesthetics: molecular correlates of voltage- and frequency-dependent sodium channel block in nerve. *J Pharmacol Exp Ther* 1979; **210**: 446–52

11 Haydon DA, Kimura JE. Some effects of *N*-pentane on the sodium and potassium currents of the squid giant axon. *J Physiol* 1981; **312**: 57–70

12 Haydon DA, Urban BW. The action of hydrocarbons and carbon tetrachloride on the sodium current of the squid giant axon. *J Physiol* 1983; **338**: 435–50

13 Morgan GE Jr, Mikhail MS. Nonvolatile anesthetic agents In: *Clinical Anesthesiology*, 2nd Edn. Stamford, Connecticut: Appleton & Lange, 1996; 128–48

14 Mantz J, Lecharny JB, Laudenbach V, Henzel D, Peytavin G, Desmonts JM. Anesthetics affect the uptake but not the depolarization-evoked release of GABA in rat striatal synaptosomes. *Anesthesiology* 1995; **82**: 502–11

15 Nordmark J, Rydqvist B. Local anaesthetics potentiate GABA mediated Cl^- currents by inhibiting GABA uptake. *Neuroreport* 1997; **8**: 465–8

16 Covino BG. Local anesthetic agents. In: Attia RR, Grogono AW, Domer FR, eds. *Practical Anesthetic Pharmacology*. Norwalk, CO: Appleton-Century-Crofts, 1991; 55–77

British Journal of Anaesthesia 89 (6) 853–6 (2002)

Sevoflurane anaesthesia in children after induction of anaesthesia with midazolam and thiopental does not cause epileptiform EEG

K. Nieminen, S. Westerèn-Punnonen, H. Kokki*[†], H. Yppärilä, A. Hyvärinen and J. Partanen

Department of Anaesthesiology and Intensive Care, Department of Clinical Neurophysiology and Department of Otorhinolaryngology, Kuopio University Hospital, PO Box 1777, FIN-70211 Kuopio, Finland

**Corresponding author: Hannu Kokki, Kuopio University Hospital, PO Box 1777, FIN-70211 Helsinki, Finland*

Background. Sevoflurane is a methyl ether anaesthetic commonly used for induction and maintenance of general anaesthesia in children. Sevoflurane is a non-irritant and acts quickly so induction is usually calm. However, inhalation induction with high concentrations of sevoflurane can cause convulsion-like movements and seizure-like changes in the electroencephalogram (EEG). Little is known about the EEG during maintenance of anaesthesia with sevoflurane, so we planned a prospective trial of sevoflurane maintenance after i.v. induction with benzodiazepine and barbiturate, which is another common induction technique in children.

Methods. EEG recordings were made before premedication with midazolam (0.1 mg kg^{-1} i.v.), during induction of anaesthesia with thiopental (5 mg kg^{-1}), and during maintenance with sevoflurane (2% end-tidal concentration in air/oxygen without nitrous oxide) in 30 generally healthy, 3- to 8-year-old children having adenoids removed. Noise-free EEG data of good quality were successfully recorded from all 30 children.

Results. Two independent neurophysiologists did not detect epileptiform discharges in any of the recordings.

Conclusion. Premedication with midazolam, i.v. induction with thiopental and maintenance of anaesthesia with 2% sevoflurane in air does not cause epileptiform EEG patterns in children.

Br J Anaesth 2002; **89**: 853–6

Keywords: anaesthetics i.v., thiopental; anaesthetics volatile, sevoflurane; children; hypnotics benzodiazepine, midazolam; monitoring, electroencephalography

Accepted for publication: July 7, 2002

Sevoflurane is a rapid, potent, halogenated volatile anaesthetic with low solubility in blood. It is a non-irritant, of low pungency and children accept it easily. Therefore, sevoflurane is often used to induce and maintain anaesthesia in children.[1]

Although sevoflurane is generally well tolerated, adverse effects have been reported. For example, coughing, laryngospasm, agitation and excitement may occur during sevoflurane anaesthesia.[1] In some reports of inhalation induction with high concentrations, seizure-like electrical activity or movement has been reported with an incidence of 20–88%.[2–5] However, agitation during sevoflurane anaesthesia is not usually associated with seizures[6] and sevoflurane is not contraindicated in patients with epilepsy.[7]

Although induction of anaesthesia with sevoflurane has been investigated extensively, less is known about the electroencephalogram (EEG) during maintenance of anaesthesia with sevoflurane. In our hospital we induce anaesthesia with i.v. midazolam and thiopental, and then maintain anaesthesia with sevoflurane. Because both midazolam and thiopental may reduce the likelihood of seizures, we studied this anaesthesia regimen, looking for epileptiform changes in the EEG during anaesthesia induction and maintenance. We recorded EEG before premedication and continuously during anaesthesia induction and maintenance until electrocautery was used for the first time.

Methods

We studied 30 children (aged 3–8 years) with ASA I physical status who were to undergo adenoidectomy in our day-case surgery unit. Patients were excluded if they had epilepsy, a history of febrile convulsions, asthma, or kidney

---

[†] *Declaration of interest:* Dr Kokki has been paid by Abbott for lecture fees.

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

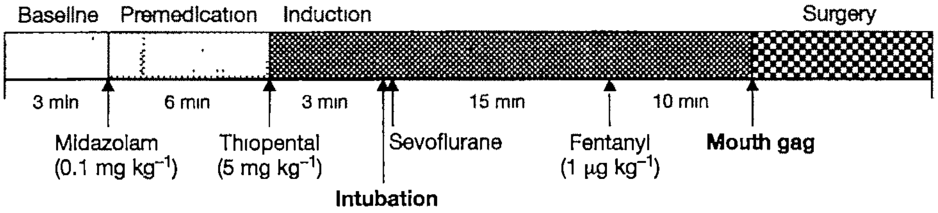


Fig 1 Flowchart of the study

or liver dysfunction. Data were collected between October 2000 and February 2001. The study was approved by the Ethics Committee of Kuopio University Hospital and was conducted in accordance with the latest revision of the Declaration of Helsinki.[8] All parents and children old enough were informed and gave written consent.

All children received the same anaesthesia. EMLA cream (Astra, Södertelje, Sweden) was used for skin analgesia. After baseline measurements, midazolam (0.1 mg kg^{-1} i.v.) was given. Five minutes later, anaesthesia was induced with thiopental (5 mg kg^{-1} i.v.) and tracheal intubation was facilitated by *cis*-atracurium (0.1 mg kg^{-1} i.v.). Patients were ventilated with oxygen in air to maintain an end-tidal carbon dioxide partial pressure of 4.8–5.5 kPa. Sevoflurane was started 3 min after the induction and adjusted to keep the end-tidal concentration at 2%. Fentanyl (1 µg kg^{-1} i.v.) was given before surgery started. On completion of surgery, neuromuscular block was antagonized with neostigmine and glycopyrrolate. All children were given 5% glucose in 0.3% saline for intraoperative fluid maintenance. Intraoperative, non-invasive arterial pressure, electrocardiography, peripheral oxygen saturation, inspiratory and end-tidal oxygen, carbon dioxide and sevoflurane concentrations were monitored continuously by Cardiocap/5 (Datex-Ohmeda, Helsinki, Finland).

The EEG was recorded with a five-channel EEG measuring machine, EMMA (developed at the Department of Clinical Neurophysiology, Kuopio University Hospital, Kuopio, Finland). The EMMA EEG machine has been validated and there are no differences compared with a standard EEG machine that could affect the results.[9] Ag/AgCl electrodes were placed on the scalp according to the international 10–20 system. The EEG signal was recorded from the electrodes F4 and Fz which were referenced to C4′ (2 cm behind C4). Additional M1 and O2 electrodes referenced to C4′ were used for the first 11 patients. Electrode–skin impedances were <5 kΩ. The signal was amplified, digitized at a rate of 279 Hz and stored on a PC for off-line analysis. Baseline EEG was recorded before premedication. EEG was then recorded continuously until electrocautery was used for the first time. Two children received midazolam (0.1 mg kg^{-1} i.v.) and one child thiopental (1 mg kg^{-1} i.v.) before baseline recordings to facilitate connection of electrodes. These three children were included in the EEG analysis as agreed in the trial protocol.

The EEG signal was inspected by two independent neurophysiologists (S W-P, J P) for detecting possible epileptiform discharges. They knew the purpose of the study, but the records were viewed with no patient details given. The EEG signal was classified as fast beta activity (>13 Hz), alpha activity (8–13 Hz), theta activity (5–8 Hz) and delta activity (≤4 Hz). Figure 1 shows the timing of the events during the EEG record.

After 30 min of EEG recording, a mouth gag was inserted and the adenoids were removed using a curettage technique. Haemostasis was controlled with temporary nasopharyngeal packs and by suction electrocautery when needed. After surgery, children were transferred to the post-anaesthesia care unit for continuous monitoring of vital signs and measurement of pain. Postoperative pain was treated with ketoprofen (2 mg kg^{-1} i.v.), and fentanyl (1 µg kg^{-1} i.v.) was used for rescue analgesia. All children were discharged after 3–4 h.

Statistical analysis

A sample size of 30 patients is commonly used in this kind of study,[2–5] and was considered sufficient also for the present trial to detect a clinically important incidence of EEG abnormality. A sample size of 30 children has a 0.8 power to detect an incidence >27% at a significance level of 0.05.

Friedman's test was used for statistical comparison of repeated measures of arterial pressure and heart rate, followed by Wilcoxon's signed-rank test with Bonferroni correction if indicated. Significance was set at $P<0.05$.

Data are presented as mean (SD) and range as appropriate.

Results

The patients' characteristics are summarized in Table 1. All the parents/children asked gave consent and participated in the trial. Apart from two children who received midazolam and one child who received thiopental before the baseline measurements were taken, there were no other significant protocol violations. All 30 children were included in the EEG analysis.

Table 1 Patient characteristics. Data are number of cases, mean (SD) and [range]

Sex (M/F)	10/20
Weight	21 (7) kg [12–48]
Height	112 (10) cm [96–140]
Age	62 (18) month [37–104]

Noise-free EEG data of good quality was successfully recorded for every child. Baseline EEG was normal and the background activity was according to age. A few seconds after midazolam injection, beta activity was seen in the EEG of each patient. Thiopental injection caused a prompt appearance of high amplitude delta waves. This delta activity gradually decreased over 3 min and had almost disappeared before sevoflurane was started.

After starting sevoflurane inhalation the EEG showed mainly mixed delta activity with various amounts of beta waves superimposed. Occasionally, this pattern resembled delta with spikes, but epileptiform spikes were not detected. No other epileptiform EEG pattern, such as suppression with spikes, rhythmic polyspikes or periodic epileptiform discharges, was seen. During anaesthesia with sevoflurane, the EEG showed mixed delta/theta/beta activity (Fig. 2).

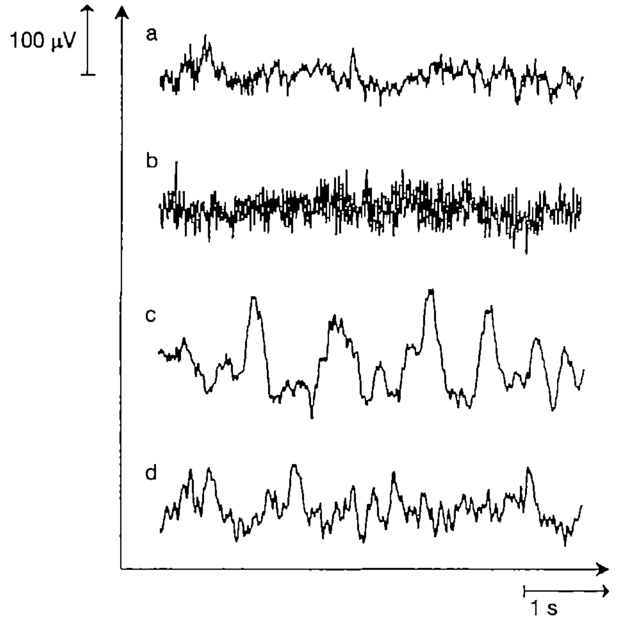


Fig 2 An EEG recording of a 6-yr-old girl Time window is 5 s, derivation F4–Fz (a) Baseline EEG with eyes open, (b) beta activity after midazolam, (c) high amplitude delta waves after thiopental induction, (d) mixed delta/theta/beta activity during sevoflurane maintenance.

Discussion

In clinical trials, volatile anaesthetics are commonly given as single agents to avoid interaction with other drugs. However, this is not often clinical routine so we designed the present study to determine whether sevoflurane may be used safely for anaesthesia maintenance following i.v. induction. It seems that the regimen used (i.e. premedication with midazolam, induction with thiopental and anaesthesia maintenance with sevoflurane in oxygen/air) does not cause any epileptiform activity. Our results suggest that sevoflurane administration is compatible with midazolam, thiopental, fentanyl and *cis*-atracurium as commonly used in paediatric anaesthesia.

Midazolam is frequently used in paediatric anaesthesia.[10] In addition to anxiolysis and sedation, midazolam also has a significant anticonvulsant effect[11] that makes it appropriate for co-induction with sevoflurane. Both midazolam and thiopental increase the threshold for convulsions and reduce the incidence of EEG abnormality. An increase in beta activity seen after midazolam injection was expected because benzodiazepines are known to enhance beta activity.[12]

Sevoflurane can cause epileptiform EEG signals when used for inhalation induction with hyperventilation. Vakkuri and co-workers[4] used high sevoflurane concentrations (8% in nitrous oxide in oxygen) for anaesthesia induction and found several forms of abnormal EEG. Suppression with spikes, rhythmic polyspikes and periodic epileptiform discharges were found in most children; the incidence of these abnormalities was 88%. In contrast, Constant and co-workers[6] did not find any seizures in children during inhalation induction with three different regimens. After midazolam premedication children were given either a rapid induction with 7% sevoflurane in oxygen; induction with incremental concentrations of sevoflurane of 2, 4, 6 and 7% in oxygen; or induction with halothane. They found a difference between sevoflurane and halothane. With sevoflurane, sharp slow waves with very fast rhythms were commonly seen, whereas slow waves and fast rhythms were observed with halothane.

Recently, an increase in the heart rate has been shown to develop during inhalation induction with various volatile anaesthetics, and higher heart rates are particularly common during concurrent epileptiform discharges.[4 6 13 14] In the present study the heart rate did not increase with sevoflurane inhalation. However, a significant increase in the heart rate and mean arterial pressure was seen during intubation, application of a mouth gag and surgical incision. This indicates that the anaesthesia used in the present study was insufficient to completely abolish the haemodynamic responses to nociceptive stimuli.

In previous studies, epileptiform potentials were seen during induction of anaesthesia with high sevoflurane concentrations. In the present study the end-tidal sevoflurane concentration was set at 2% and no EEG problems occurred. It is not clear whether the lack of epileptiform potentials is because thiopental and midazolam were given or because a lower dose of sevoflurane was used.

We stopped recording when electrocautery was used for the first time and no EEG was recorded during emergence from anaesthesia. Because a high incidence of agitation during emergence from sevoflurane anaesthesia has been reported in previous trials,[1] it would be interesting in future to record EEG during recovery from anaesthesia.

We conclude that anaesthesia maintenance with 2% sevoflurane in oxygen/air in children after i.v. induction with midazolam and thiopental does not elicit seizure-like changes in the EEG.

References

1. Goa KL, Noble S, Spencer CM. Sevoflurane in paediatric anaesthesia. *Paediatr Drugs* 1999; **1**: 127–53
2. Woodforth IJ, Hicks RG, Crawford MR, *et al*. Electroencephalographic evidence of seizure under deep sevoflurane anesthesia in a nonepileptic patient. *Anesthesiology* 1997; **87**: 1579–82
3. Komatsu H, Taie S, Endo S, *et al*. Electrical seizures during sevoflurane anesthesia in two pediatric patients with epilepsy. *Anesthesiology* 1994; **81**: 1535–7
4. Vakkuri A, Yli-Hankala A, Sarkela M, *et al*. Sevoflurane mask induction of anaesthesia is associated with epileptiform EEG in children. *Acta Anaesthesiol Scand* 2001; **45**: 805–11
5. Adachi M, Ikemoto Y, Kubo K, *et al*. Seizure-like movements during induction of anaesthesia with sevoflurane. *Br J Anaesth* 1992; **68**: 214–15
6. Constant I, Dubois M-C, Piat V, *et al*. Changes in electroencephalogram and autonomic cardiovascular activity during induction of anesthesia with sevoflurane compared with halothane in children. *Anesthesiology* 1999; **91**: 1604–15
7. *British National Formulary*. London: BMA, 2000; **40**: 572–3
8. World Medical Association Declaration of Helsinki. *Ethical Principles for Medical Research Involving Human Subjects*. 52nd World Medical Association, General Assembly, Edinburgh, UK, October 2000
9. Ypparilä H, Karhu J, Westeren-Punnonen S, *et al*. Evidence of auditory processing during postoperative propofol sedation. *Clin Neurophysiol* 2002; **113**: 1357–64
10. Brosius K, Bannister C. Effect of oral midazolam premedication on the awakening concentration of sevoflurane, recovery times and bispectral index in children. *Paediatr Anaesth* 2001; **11**: 585–90
11. Scott R, Besag F, Boyd S, Berry D, Neville B. Buccal absorption of midazolam: pharmacokinetics and EEG pharmacodynamics. *Epilepsia* 1998; **39**: 290–4
12. Holmes G, Korteling F. Drug effects on the human EEG. *Am J EEG Technol* 1993; **33**: 1–26
13. Jantti V, Yli-Hankala A. Correlation of instantaneous heart rate and EEG suppression during enflurane anaesthesia: synchronous inhibition of heart rate and cortical electrical activity? *Electroencephalogr Clin Neurophysiol* 1990; **76**: 476–9
14. Yli-Hankala A, Jantti V. EEG burst-suppression pattern correlates with the instantaneous heart rate under isoflurane anaesthesia. *Acta Anaesthesiol Scand* 1990; **34**: 665–8

British Journal of Anaesthesia 89 (6). 857–62 (2002)

Esmolol prevents movement and attenuates the BIS response to orotracheal intubation†

C. Menigaux[1], B. Guignard[1], F. Adam[1], D. I. Sessler[2], V. Joly[1] and M. Chauvin[1]*

[1]*Département d'Anesthésie-Réanimation, Ambroise Pare Hôpital, 9 Avenue Charles de Gaulle, F-92100 Boulogne-Billancourt, France.* [2]*Outcomes Research® Institute and Department of Anesthesiology, University of Louisville, Kentucky, USA; Ludwig Boltzmann Anesthesia Institute, University of Vienna, Vienna, Austria*

**Corresponding author. E-mail: marcel.chauvin@apr.ap-hop-paris.fr*

Background. Beta-adrenergic agonists enhance behavioural and electroencephalographic arousal reactions. We explored whether adding esmolol, a short-acting β_1-adrenoceptor antagonist, to propofol anaesthesia modified the bispectral index (BIS) during induction of anaesthesia and orotracheal intubation.

Methods. Fifty patients were randomly allocated, in a double-blind fashion, to receive esmolol 1 mg kg^{-1} followed by 250 µg kg^{-1} min^{-1} or saline (control). Esmolol or saline was started 6 min after a target-controlled infusion (TCI) of propofol (effect-site concentration 4 µg ml^{-1}). After loss of consciousness, and before administration of vecuronium 0.1 mg kg^{-1}, a tourniquet was applied to one arm and inflated to 150 mm Hg greater than systolic pressure. Eleven minutes after the TCI began, the trachea was intubated; gross movement within the first min after orotracheal intubation was recorded. BIS was recorded at 10-s intervals. Mean arterial pressure (MAP) and heart rate were measured non-invasively every min.

Results. There were no intergroup differences in BIS, heart rate or MAP before laryngoscopy. BIS increased significantly after orotracheal intubation (compared with the pre-laryngoscopy values) in the control group only, with a maximum increase of 40 (SD 18)% *vs* 8 (11)% in the esmolol group ($P<0.01$). Maximum changes in heart rate [45 (19)% *vs* 23 (14)%] and MAP [62 (24)% *vs* 45 (23)%] with orotracheal intubation were also significantly greater in the control group than in the esmolol group. More patients in the control than in the esmolol group moved after orotracheal intubation (23 *vs* 12, $P<0.01$).

Conclusion. Esmolol not only attenuated haemodynamic and somatic responses to laryngoscopy and orotracheal intubation, but also prevented BIS arousal reactions in patients anaesthetized with propofol.

Br J Anaesth 2002; **89**: 857–62

Keywords: anaesthetic techniques, i.v.; intubation tracheal, haemodynamic changes; monitoring, bispectral index; potency, anaesthetic

Accepted for publication: July 29, 2002

Noxious stimulation during general anaesthesia causes various reactions, including movement, sympathetic nervous system stimulation, and arousal reactions that may be detected on the electroencephalogram (EEG).[1–3] For example, laryngoscopy and orotracheal intubation increase the bispectral index (BIS), as well as haemodynamic variables.[2] Both BIS and the haemodynamic responses to noxious stimulation are attenuated by opiate administration.[1 2] These results suggest that BIS monitoring can help to detect inadequate analgesia during general anaesthesia.

Esmolol, a short-acting β_1-adrenoceptor antagonist, produces dose-dependent attenuation of the adrenergic response to laryngoscopy and orotracheal intubation.[4] However, previous studies assessing the effectiveness of

---

†*Declaration of interest* Supported by NIH Grant GM 58273 (Bethesda, MD, USA), the Joseph Drown Foundation (Los Angeles, CA, USA), and the Commonwealth of Kentucky Research Challenge Trust Fund (Louisville, KY, USA) None of the authors has any personal financial interest in this research

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

esmolol in blunting the haemodynamic alterations induced by laryngoscopy and orotracheal intubation failed to monitor electrical activity of the brain. Only a few studies have evaluated the effect of interaction between β-adrenoceptor antagonists and anaesthetics on BIS.[5 6] They raised the possibility that esmolol administration may mask inadequate anaesthesia.

It is also known that esmolol decreases the amount of anaesthesia required to prevent movement in response to skin incision.[7 8] Although a correlation between BIS and movement has been observed under some circumstances,[9] no relationship has been observed in other studies.[10 11] A poor relationship between movement and BIS is understandable since EEG measures cortical activity, whereas movement in response to noxious stimulation originates in the spinal cord.[12] Our purpose was therefore to determine whether preventing haemodynamic responses during laryngoscopy and orotracheal intubation with esmolol simultaneously ameliorates somatic and BIS arousal reactions.

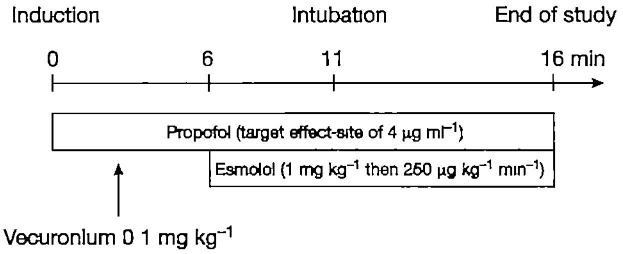

Induction
Intubation
End of study
0
6
11
16 min
Propofol (target effect-site of 4 μg ml⁻¹)
Esmolol (1 mg kg⁻¹ then 250 μg kg⁻¹ min⁻¹)
Vecuronium 0 1 mg kg⁻¹

Fig 1 Details of study.

Materials and methods

After approval from the Medical Ethics Committee of the Hôpital Ambroise Pare, we obtained written informed consent from 50 patients. All were ASA physical status I or II, aged 18–70 yr, and scheduled for elective non-cranial surgery. Exclusion criteria included neurological, cardiac or metabolic disease, chronic hypertension, asthma or reactive airway disease, cardiovascular or β-blocker medication, routine use of analgesics or hypnotic medication, drug or alcohol abuse, and obesity (>130% of ideal body weight).

Patients were assigned randomly, in a double-blind fashion, to one of two groups (25 patients per group): control or esmolol. Group allocations were based on computer-generated codes. The hospital pharmacist prepared suitable syringes for each patient: a 10-ml syringe containing either isotonic sodium chloride (saline) or esmolol 100 mg in saline for the initial bolus, and a 50 ml syringe containing either saline or esmolol 250 mg diluted in saline for the continuous infusion. Patients and personnel involved in patient management and data collection were unaware of the group assignment.

Figure 1 shows the time line for the study protocol. No sedative premedication was given. After preoxygenation, the subjects were anaesthetized with i.v. propofol. The patients were manually ventilated to maintain end-tidal carbon dioxide concentration between 30 and 35 mm Hg until laryngoscopy and orotracheal intubation; subsequently, they were mechanically ventilated with oxygen 40%. Propofol was administered via a computer-assisted infusion device (Fresenius Vial Medical, Brezins, France) using a program written in Visual Basic® 5 (Microsoft Corporation, Redmond, OR, USA) by one of the investigators (BG). The pharmacokinetic set published by Marsh and colleagues[13] was used to estimate target effect-site concentrations of propofol. The plasma effect-site equilibrium rate constant (K_{eo}) value used for propofol was 0.638 min^{-1}.[13] Propofol was administered to a target effect-site concentration of 4 μg ml^{-1} (i.e. 2 mg kg^{-1} bolus followed by 225 μg kg^{-1} min^{-1}) during the entire study period.

The isolated-arm technique was used to evaluate patient movement after administration of the neuromuscular blocking agent.[2] After loss of consciousness, an arm tourniquet was inflated to 150 mm Hg above systolic pressure; vecuronium 0.1 mg kg^{-1} was then given. Six minutes after the propofol target-controlled infusion (TCI) began, the esmolol group was given a bolus of esmolol 1 mg kg^{-1}, followed by an infusion of 250 μg kg^{-1} min^{-1}. The control group was given a comparable volume of saline. The trachea was intubated 11 min after the start of the propofol infusion. The same investigator (CM) performed the laryngoscopy and orotracheal intubation in every patient, while a second investigator (BG) noted the duration of laryngoscopy and orotracheal intubation, defined as the time from mouth opening until inflation of the tracheal tube balloon. This second examiner also assessed patient movement in response to laryngoscopy and orotracheal intubation. A positive response was defined as gross purposeful movement of the arm with the tourniquet attached within 1 min of orotracheal intubation. Hypotension was defined as a mean arterial pressure (MAP) <60 mm Hg and bradycardia as heart rate <50 beats min^{-1}. The study ended 16 min after starting the propofol.

Before induction of anaesthesia, silver/silver chloride pre-gelled electrodes (Aspect Medical Systems, Natick, MA, USA) were applied to the left and right frontal (Fp1 and Fp2) regions and referred to a vertex electrode (Cz). We confirmed that electrode impedance was <2000 Ω. The EEG was recorded continuously using an Aspect A-1000 EEG monitor (Aspect Medical Systems, Natick, MA, USA), which also continuously computed the BIS (revision 3.3). A BIS value was generated every 10 s. Arterial pressure and heart rate were measured non-invasively every minute using a Cardiocap monitor (Datex, Helsinki, Finland), and acquired simultaneously with the EEG using multi-serial interfaces between the monitors and a personal computer. All acquired data were stored on disk for subsequent analysis.

The BIS values given are the mean of six measurements taken at each data point. The recordings were taken before induction; before the start of esmolol or saline; 1, 3 and 5 min (pre-laryngoscopy) after the start of the esmolol infusion; and 1, 2 and 5 min after orotracheal intubation.

Changes in BIS, heart rate and MAP with orotracheal intubation (ΔBIS, ΔHR and ΔMAP, respectively) were defined as the differences between the pre-laryngoscopy values and the maximal value obtained for each variable within the first 5 min after orotracheal intubation.

On the first postoperative day, patients were asked whether they recalled any intraoperative events.

Statistical analysis

All statistical analyses were performed using Statview (Version 5.0, SAS Institute Inc., Cary, NC, USA). Physical characteristics, durations of laryngoscopy and orotracheal intubation, and maximum ΔBIS, ΔHR and ΔMAP during the 5 min following orotracheal intubation were evaluated using analysis of variance (ANOVA). The BIS, heart rate and MAP at each time point in each group and ΔBIS, ΔHR and ΔMAP from baseline were analysed using ANOVA and repeated-measures ANOVA. To evaluate the stability of the BIS recordings, the coefficients of variation of the BIS values obtained within the 1-min periods were calculated for each individual.

Fisher's exact test was used to compare the proportion of patients with movement in each group. When a difference in proportions was found betwen the groups, pair-wise comparisons were performed. Results are presented as mean (SD); $P<0.05$ was considered statistically significant.

Table 1 Physical characteristics of the control and esmolol groups. Data are mean (SD or range)

	Control n=25	Esmolol n=25
Age (yr)	36 (18–54)	37 (19–53)
Weight (kg)	71 (15)	68 (16)
Height (cm)	172 (11)	173 (10)
Sex (m/f)	18/7	15/10
Intubation duration (s)	37 (21)	47 (28)

Results

No significant differences were found between the esmolol and control groups with respect to age, weight, height, sex ratio or the duration of laryngoscopy and orotracheal intubation (Table 1). BIS, heart rate and MAP during the pre-induction period were also similar in the two groups (Table 2).

In all patients, BIS values obtained within each 1-min period before laryngoscopy were stable, with a coefficient of variation that did not exceed 10%. BIS values, heart rate and MAP did not differ significantly between the two groups before laryngoscopy (Table 2). Furthermore, BIS values remained stable from injection of esmolol or saline to laryngoscopy, with a coefficient of variation of less than 15% in each patient (Fig. 2).

Laryngoscopy and orotracheal intubation were associated with a significant increase in BIS (compared with the pre-laryngoscopy values) in the control group only (Table 2 and Fig. 2), with a maximal increase of 40 (SD 18)% (range 6–90%), compared with 8 (11)% (range 0–48%) in the esmolol group ($P<0.01$; Fig. 3).

Maximum ΔHR and ΔMAP after orotracheal intubation from pre-stimulus values were significant ($P<0.05$) for both groups; however, these changes were significantly greater in the control group (MAP: 62 (SD 24)% *vs* 45 (23)%, $P<0.01$; heart rate: 45 (19)% *vs* 23 (14)%, $P<0.05$; Fig. 3). More patients moved in response to laryngoscopy and orotracheal intubation in the control group (23 of 25) than in the esmolol group (12 of 25) ($P<0.01$). ΔBIS, ΔHR and ΔMAP did not correlate with the presence or absence of movement in the esmolol group (Fig. 3). Neither hypotension nor bradycardia was noted in either group. None of the patients reported recall of intraoperative events when questioned on the first postoperative day.

Discussion

Esmolol is clinically effective in attenuating adrenergic responses to a number of noxious intraoperative stimuli, including laryngoscopy and orotracheal intubation.[4] The present study demonstrated that esmolol not only attenuated the haemodynamic and gross motor responses to laryngoscopy and orotracheal intubation, but also prevented arousal

Table 2 Bispectral index (BIS), heart rate and mean arterial pressure (MAP) for the control (n=25) and esmolol (n=25) groups. Values are mean (SD) $^{*}P<0.001$ *vs* pre-esmolol value; $^{\dagger}P<0.05$, $^{\ddagger}P<0.001$ *vs* pre-laryngoscopy values; $^{\S}P<0.05$, $^{\P}P<0.001$ *vs* control group. OTI=orotracheal intubation

	BIS		Heart rate		MAP	
	Control	Esmolol	Control	Esmolol	Control	Esmolol
Pre-induction	97 (1)	97 (1)	71(11)	70 (13)	86 (14)	88 (12)
Pre-esmolol	44 (6)	44 (8)	68 (9)	68 (11)	81 (17)	83 (14)
Pre-laryngoscopy	45 (6)	43 (6)	69 (7)	64 (11)	79 (15)	77 (14)
1 min after OTI	61 (10)$^{\ddagger *}$	43 (7)¶	96 (18)$^{\ddagger *}$	75 (8)$^{\ddagger \P}$	130 (26)$^{\ddagger *}$	109 (16)$^{\ddagger \S}$
2 min after OTI	53 (10)‡	41 (9)¶	83 (14)‡	70 (9)$^{\dagger \P}$	109 (22)‡	97 (18)$^{\ddagger \S}$
5 min after OTI	47 (9)	40 (6)¶	74 (13)	67 (11)§	90 (16)	86 (15)

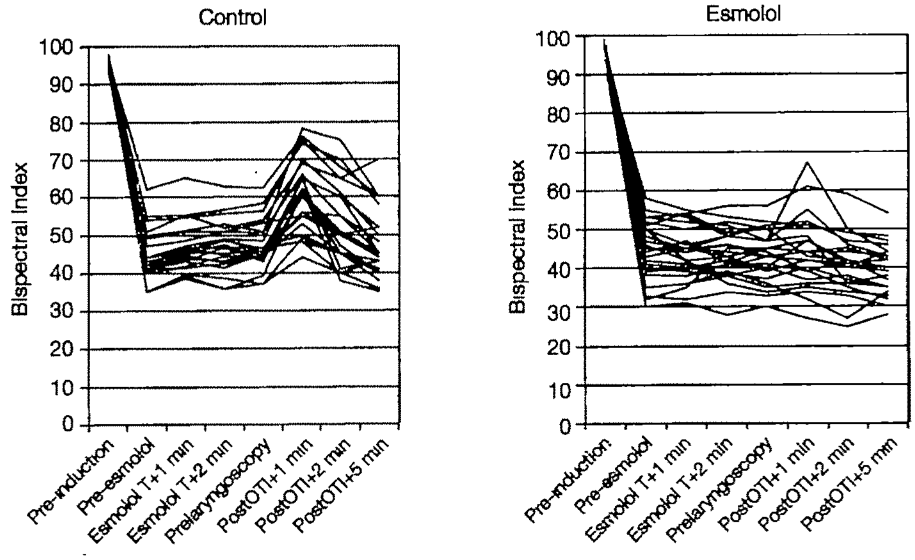


Fig 2 Individual bispectral index values: before induction; 1 min before esmolol, 1, 3 and 5 mins (pre-laryngoscopy) after the start of esmolol infusion; and 1, 2 and 5 min after orotracheal intubation (OTI).

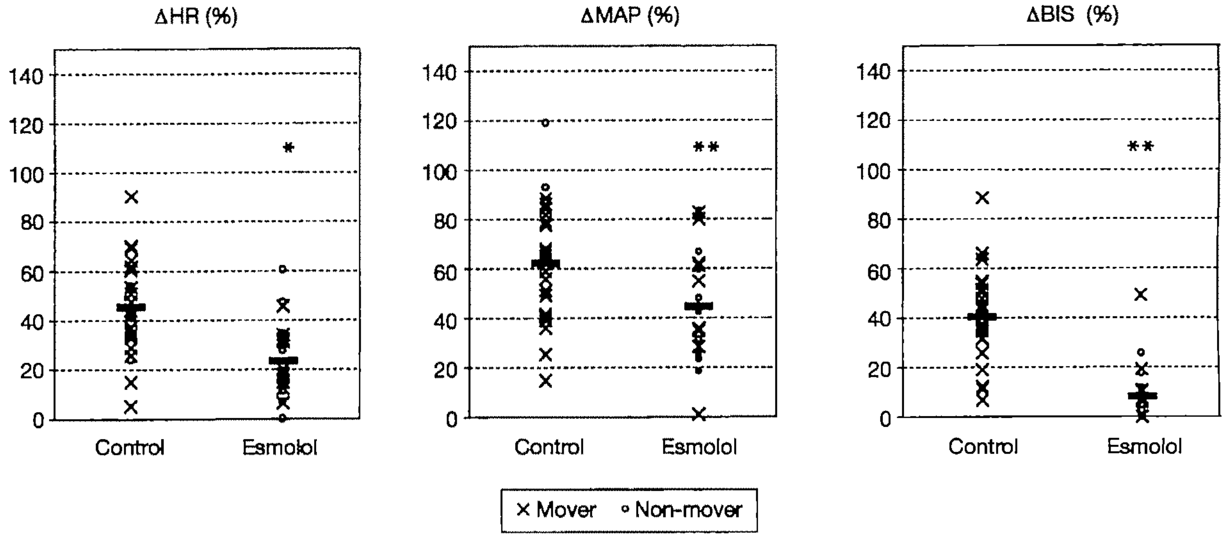


Fig 3 Maximum changes of heart rate (ΔHR), mean arterial pressure (ΔMAP), and bispectral index (ΔBIS) after orotracheal intubation expressed as percentage of values recorded before laryngoscopy in the control and esmolol groups. Each symbol represents an individual patient. The horizontal bars denote mean values for each variable. *$P<0.05$; **$P<0.01$ *vs* control group.

reactions, as indicated by attenuated BIS increases after the stimulation of laryngoscopy and orotracheal intubation. Our current data support those we reported previously with high-dose remifentanil.[2] Together, these findings suggest that esmolol and opioids similarly influence BIS during propofol anaesthesia.

There is a dose-dependent risk of hypotension and bradycardia before laryngoscopy when esmolol is combined with anaesthesia induction agents.[4] However, the esmolol regimen used in the present study did not result in any deleterious haemodynamic effects. We did not use opioids, which may have decreased heart rate and MAP before laryngoscopy in other studies.[4 14] Compared with earlier reports,[4 14] esmolol was more effective in this study in controlling tachycardia than the pressor response to laryngoscopy and orotracheal intubation. This difference is consistent with the different mechanisms involved in each response: bradycardia results from a direct cardiac effect of esmolol whereas hypotension results from a gradual decrease in renin release.[15] As might be expected, the time required to obtain 90% of the maximum decrease in heart rate (4.8 min) is far shorter than that for the same decrease in MAP (42 min).[15]

Esmolol decreased the incidence of movement in response to laryngoscopy and orotracheal intubation. These results are consistent with reports that esmolol reduces the propofol concentration required to prevent movement in response to skin incision.[7] In that study, propofol was combined with nitrous oxide and morphine premedication.[7] Interaction between any of the anaesthetic components, specifically with nitrous oxide or morphine and esmolol, may have caused the effect. In fact, the same group found that esmolol had no effects on isoflurane minimum alveolar concentration (MAC) alone, but that MAC was decreased when esmolol was given along with alfentanil, suggesting a possible potentiation of opioid action by esmolol.[8] That study only evaluated movement and haemodynamic responses to skin incision. In contrast, our current study indicates that propofol combined with esmolol alone, at a similar dose to that used by Johansen and co-workers,[8] blunted nociceptive reactions to laryngoscopy and orotracheal intubation, including changes in BIS, as well as the autonomic and somatic responses. It is unclear whether our results are inconsistent with those of Johansen and co-workers[8] because there were differences in the design and anaesthetic regimens between the two studies. However, our results are consistent with two other studies, each of which demonstrated that esmolol can be used as an alternative to opioids for maintaining haemodynamic,[6 16] and BIS[6] stability during general anaesthesia.

Addition of esmolol to general anaesthesia with propofol did not affect BIS before laryngoscopy. This observation suggests that esmolol does not modify BIS during general anaesthesia when substantial sympathetic activation is unlikely. It seems likely that esmolol has no anaesthetic effect *per se*; instead, it acts mainly via β-adrenergic block and is thus effective only during sympathetic activation. These results are consistent with a recent study reporting that the propofol blood concentration preventing response to command was unaltered by esmolol.[17] In contrast, Johansen[18] showed that esmolol suppressed the EEG, with a decrease in BIS and an increase in the burst suppression ratio during propofol/alfentanil anaesthesia. However, in the latter study,[18] surgical stimuli were not controlled and it seems likely that esmolol blunted the adrenergic response to them.

Our results and previous studies[5 6] clearly indicate that β-adrenoceptor antagonists not only block cardiovascular stress responses after noxious stimulation, which could mask inadequate anaesthesia, but also increase the antinociceptive component of anaesthesia. The mechanism for this effect remains unclear. One explanation may be a central antinociceptive effect of β-adrenoceptor block. Consistent with this hypothesis is the finding that i.v. esmolol[19] decreases nociceptive behaviour in rats after formalin injection, as did intrathecal ONO 1101,[20] another β_1-adrenoreceptor antagonist. Noxious stimulation is transmitted through the spinal cord, the brainstem reticular formation and the thalamus to the cerebral cortex, where it evokes an EEG arousal response. Beta-adrenoceptors are present in various parts of the reticular activating system, particularly the medial septal region of the basal forebrain.[21] Infusion of β-adrenoceptor agonists into this region elicits enhancement of behavioural and EEG indices of waking in animals.[21] Conversely, infusion of β-adrenoceptor antagonists decreases EEG indices of arousal.[21] Similarly in humans, infusion of isoprenaline[22] or epinephrine[23] causes clinical signs of arousal associated with an increase in BIS.[23] Additionally, BIS levels are significantly correlated with plasma norepinephrine concentrations after oral diazepam premedication.[24] This finding suggests that the noxious stimulation of laryngoscopy and orotracheal intubation increases central catecholamine concentrations, and that esmolol prevents the increase in BIS in response to laryngoscopy and orotracheal intubation by blocking β-adrenoceptors within the reticular formation. However, the pharmacokinetics of esmolol do not entirely support this hypothesis. Esmolol is hydrophilic, as is atenolol;[25] and like atenolol, it probably does not readily cross the blood–brain barrier.[26] The brain:plasma ratio for esmolol is unknown, but it was found to be 0.20 for atenolol, compared with 26 and 50, respectively for the lipophilic β-adrenoreceptor antagonists, propranolol and oxprenolol.

Another explanation may be an alteration of the pharmacokinetics of propofol by esmolol. Doses of esmolol similar to those we used were not found to change the performance of the propofol TCI device in two studies,[7 18] whereas it increased the bias and reduced the inaccuracy of the TCI device in another.[17] Our finding, that BIS values before laryngoscopy were similar in the two groups, does not support this theory. In addition, esmolol has been shown to control intraoperative nociceptive responses during desflurane anaesthesia in a similar way to a comparative group that received desflurane and an opioid in the anaesthetic regimen.[6] In another study, patients β-blocked with atenolol required less fentanyl and isoflurane than unblocked control patients to produce similar BIS values.[5] However, we did not measure propofol concentrations and thus cannot eliminate a potential pharmacokinetic interaction with esmolol. Moreover, esmolol, by attenuating the haemodynamic responses to laryngoscopy and orotracheal intubation, may have prevented the increase in cardiac output that would normally lead to redistribution of blood flow, with a resultant fall in the effect-site concentration of propofol and an increase in BIS. Thus, the exact mechanism of action of esmolol in blocking the BIS response to noxious stimulation is not understood.

In conclusion, esmolol had no significant effect on BIS before laryngoscopy and orotracheal intubation in patients anaesthetized with propofol. However, it not only attenuated the haemodynamic responses, but also prevented movement and BIS increases in response to laryngoscopy and orotracheal intubation. These results suggest that esmolol may produce a clinically important antinociceptive effect.

References

1 Iselin-Chaves IA, Flaishon R, Sebel PS, et *al*. The effect of the interaction of propofol and alfentanil on recall, loss of

consciousness, and the Bispectral Index. *Anesth Analg* 1998; **87**: 949–55

2 Guignard B, Menigaux C, Dupont X, *et al.* The effect of remifentanil on the bispectral index change and hemodynamic responses after orotracheal intubation. *Anesth Analg* 2000; **90**: 161–7

3 Ropcke H, Rehberg B, Koenen-Bergmann M, *et al.* Surgical stimulation shifts EEG concentration-response relationship of desflurane. *Anesthesiology* 2001; **94**: 390–9

4 Figueredo E, Garcia-Fuentes EM. Assessment of the efficacy of esmolol on the haemodynamic changes induced by laryngoscopy and tracheal intubation: a meta-analysis. *Acta Anaesthesiol Scand* 2001; **45**: 1011–22

5 Zaugg M, Tagliente T, Lucchinetti E, *et al.* Beneficial effects from beta-adrenergic blockade in elderly patients undergoing noncardiac surgery. *Anesthesiology* 1999; **91**: 1674–86

6 Coloma M, Chiu JW, White PF, Armbruster SC. The use of esmolol as an alternative to remifentanil during desflurane anesthesia for fast-track outpatient gynecologic laparoscopic surgery. *Anesth Analg* 2001; **92**: 352–7

7 Johansen JW, Flaishon R, Sebel PS. Esmolol reduces anesthetic requirement for skin incision during propofol/nitrous oxide/morphine anesthesia. *Anesthesiology* 1997; **86**: 364–71

8 Johansen JW, Schneider G, Windsor AM, Sebel PS. Esmolol potentiates reduction of minimum alveolar isoflurane concentration by alfentanil. *Anesth Analg* 1998; **87**: 671–6

9 Leslie K, Sessler DI, Smith WD, *et al.* Prediction of movement during propofol/nitrous oxide anesthesia. *Anesthesiology* 1996; **84**: 52–63

10 Dwyer RC, Rampil IJ, Eger EI, Bennett HL. The electroencephalogram does not predict depth of isoflurane anesthesia. *Anesthesiology* 1994; **81**: 403–9

11 Coste C, Guignard B, Menigaux C, Chauvin M. Nitrous oxide prevents movement during orotracheal intubation without affecting BIS value. *Anesth Analg* 2000; **91**: 130–5

12 Rampil IJ. Anesthetic potency is not altered after hypothermic spinal cord transection in rats. *Anesthesiology* 1994; **80**: 606–10

13 Marsh B, White M, Morton N, Kenny GN. Pharmacokinetic model driven infusion of propofol in children. *Br J Anaesth* 1991; **67**: 41–8

14 Miller DR, Martineau RJ, Wynands JE, Hill J. Bolus administration of esmolol for controlling the haemodynamic response to tracheal intubation: the Canadian Multicentre Trial. *Can J Anaesth* 1991; **38**: 849–58

15 Ornstein E, Young WL, Ostapkovich N, *et al.* Are all effects of esmolol equally rapid in onset? *Anesth Analg* 1995; **81**: 297–300

16 Smith I, Van Hemelrijck J, White PF. Efficacy of esmolol versus alfentanil as a supplement to propofol–nitrous oxide anesthesia. *Anesth Analg* 1991; **73**: 540–6

17 Orme R, Leslie K, Umranikar A, Ugoni A. Esmolol and anesthetic requirement for loss of responsiveness during propofol anesthesia. *Anesth Analg* 2002; **93**: 112–16

18 Johansen JW. Esmolol promotes electroencephalographic burst suppression during propofol/alfentanil anesthesia. *Anesth Analg* 2001; **93**: 1526–31

19 Davidson EM, Doursout MF, Szmuk P, Chelly JE. Antinociceptive and cardiovascular properties of esmolol following formalin injection in rats. *Can J Anaesth* 2001; **48**: 59–64

20 Taira Y, Kakinohana M, Kakinohana O, Okuda Y. ONO 1101, a novel ultra-short acting β1 blocker can reduce pain behaviour in the rat formalin test. *Anesthesiology* 1998; **89**: A1128

21 Berridge CW, Foote SL. Enhancement of behavioral and electroencephalographic indices of waking following stimulation of noradrenergic β-receptors within the medial septal region of the basal forebrain. *J Neurosci* 1996; **16**: 6999–7009

22 Johnson IA, Andrzejowski J, Sikiotis L. Arousal following isoprenaline. *Anaesth Intens Care* 1999; **27**: 221

23 Andrzejowski J, Sleigh JW, Johnson IAT, Sikiotis L. The effect of intravenous epinephrine on the bispectral index and sedation. *Anaesthesia* 2000; **55**: 761–3

24 Hirota K, Matsunami K, Kudo T, *et al.* Relation between bispectral index and plasma catecholamines after oral diazepam premedication. *Eur J Anaesthesiol* 1999; **16**: 516–18

25 Neil-Dwyer G, Bartlett J, McAinsh J, Cruickshank JM. β-Adrenoceptor blockers and the blood-brian barrier. *Br J Clin Pharmacol* 1981; **11**: 549–53

26 Sum CY, Yacobi A, Kartzinel R, Stampfli H, *et al.* Kinetics of esmolol, an ultra-short-acting beta blocker, and of its major metabolite. *Clin Pharmacol Ther* 1983; **34**: 427–34

British Journal of Anaesthesia 89 (6) 863–72 (2002)

Patient satisfaction with anaesthesia care: development of a psychometric questionnaire and benchmarking among six hospitals in Switzerland and Austria†‡

T. Heidegger[1]*, Y. Husemann[2], M. Nuebling[3], D. Morf[4], T. Sieber[4], A. Huth[5], R. Germann[5], P. Innerhofer[6], A. Faserl[6], C. Schubert[7], C. Geibinger[7], K. Flückiger[8], T. Coi[8] and G. Kreienbühl[1]

[1]Department of Anaesthesiology, St Gallen Cantonal Hospital, Rorschacherstrasse 95, CH-9007 St Gallen, Switzerland. [2]Picker Institute Europe, Zug, Switzerland. [3]Empirical Consulting, Freiburg, Germany. [4]Department of Anaesthesiology, Rätisches Cantonal Hospital, Chur, Switzerland. [5]Department of Anaesthesiology and Intensive Care Medicine, Landeskrankenhaus Feldkirch, Austria. [6]Department of Anaesthesiology and Critical Care Medicine, The Leopold-Franzens-University of Innsbruck, Austria. [7]Department of Anaesthesiology, St Vincent's Hospital, Linz, Austria. [8]Department of Anaesthesiology, University Hospital of Bern, Switzerland

**Corresponding author*

Background. We describe the development and comparison of a psychometric questionnaire on patient satisfaction with anaesthesia care among six hospitals.

Methods. We used a rigorous protocol: generation of items, construction of the pilot questionnaire, pilot study, statistical analysis (construct validity, factor analysis, reliability analysis), compilation of the final questionnaire, main study, repeated analysis of construct validity and reliability. We compared the mean total problem score and the scores for the dimensions: 'Information/Involvement in decision-making', and 'Continuity of personal care by anaesthetist'. The influence of potential confounding variables was tested (multiple linear regression).

Results. The average problem score from all hospitals was 18.6%. Most problems are mentioned in the dimensions 'Information/Involvement in decision-making' (mean problem score: 30.9%) and 'Continuity of personal care by anaesthetist' (mean problem score: 32.2%). The overall assessment of the quality of anaesthesia care was good to excellent in 98.7% of cases. The most important dimension was 'Information/Involvement in decision-making'. The mean total problem score was significantly lower for two hospitals than the total mean for all hospitals (significantly higher at two hospitals) ($P<0.05$). Amongst the confounding variables considered, age, sex, subjective state of health, type of anaesthesia and level of education had an influence on the total problem score and the two dimensions mentioned. There were only marginal differences with and without the influence of the confounding variables for the different hospitals.

Conclusions. A psychometric questionnaire on patient satisfaction with anaesthesia care must cover areas such as patient information, involvement in decision-making, and contact with the anaesthetist. The assessment using summed scores for dimensions is more informative than a global summed rating. There were significant differences between hospitals. Moreover, the high problem scores indicate a great potential for improvement at all hospitals.

Br J Anaesth 2002; **89**: 863–72

Keywords: anaesthesia, audit; research, anaesthesia; measurement techniques, outcome; surgery

Accepted for publication: July 30, 2002

---

†*Declaration of interest* Y. Husemann is the country manager of the Picker Institute Europe in Switzerland, which partly funded this study

‡Some of the data were presented at the meeting of the European Society of Anaesthesiology (Gothenburg, April 2001), and published in abstract form (*Eur J Anaesthesiol* 2001, 18 A12).

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Table 1 Questions on the pilot instrument

Questions	Possible answers
How long did it take you to complete this questionnaire?	Answer in minutes
How easy was it to answer this questionnaire?	Very easy, easy; quite difficult; very difficult
How easy was the questionnaire to understand?	Very easy to understand, easy to understand; quite difficult to understand; very difficult to understand
In your opinion, which questions should be made easier to understand?	Code (number) of question(s)
In your opinion, did the questionnaire ask all the important questions related to anaesthesia?	yes – completely, yes – somewhat, no
In your opinion, which questions were not asked in the questionnaire?	Space for free comment

The evaluation of the quality of patient care depends on the level at which the assessment is conducted.[1] From the patient's point of view, the quality of the outcome is of major importance.[2] The evaluation of patient satisfaction based on their subjective perception of the quality of the process forms an important part of this.[1–4] Previous projects to develop questionnaires on patient satisfaction with anaesthesia care have paid too little or no attention to two aspects.[5–7] First, the involvement of patients when developing the questions, and second, proceeding according to a strictly defined plan using a psychometric procedure with a multi-item questionnaire. The results of single-item ratings regularly produce high scores but do not reflect the true nature of the anaesthesia care.[5 8] The modern approach to quality measurement takes account not only of results from the researcher's hospital, but also compares these results with those from other hospitals in the form of benchmarking. Papers published so far from the area of anaesthesia have mainly compared anaesthesia-related incidents and complications, and not the quality of the outcome, that is, the degree of patient satisfaction with anaesthesia care.[9 10] The effects of confounding variables on patient satisfaction with anaesthesia care have been studied infrequently.[5 6] The aim of this project was to develop a psychometric questionnaire in cooperation with patients to assess their satisfaction with anaesthesia care. Furthermore, we compared the degree of patient satisfaction with different dimensions in six hospitals as a benchmarking study and, in doing so, took account of the possible effects of ten potentially confounding variables.

Methods

Generation of items

A questionnaire must contain items on all factors important to the relevant domain. This is called content validity.[11] After ethics committee approval and informed consent were obtained, we conducted four focus groups with patients who had been in the care of the anaesthetic teams because of elective surgery in the past 3 months and had been discharged more than 1 week before (January 2000). The discussion guide was formulated using an expert questionnaire (unpublished data), with the items in chronological order. The focus groups were led by a psychologist. The interviews were recorded on tape and also documented in the form of contemporaneous notes. Each group consisted of 6–11 patients. We also incorporated input from anaesthetists, nurse anaesthetists, administrative assistants and published literature.

Construction of the pilot questionnaire

For the construction of the pilot questionnaire, the items were grouped in chronological order based on the usual course of treatment. Before constructing the pilot questionnaire, we tested the items for comprehensibility and readability on lay members of staff. The questions were aimed at patients who had undergone elective surgery under general or regional anaesthesia. The pilot questionnaire contained questions on the instrument itself (Table 1), questions on the patient's overall impression, and space for free comment.

Pilot study

The pilot study was conducted in April 2000 in two tertiary care hospitals in eastern Switzerland. Patients aged 16 yr and older were enrolled in the study. Out-patients and emergency admissions were excluded. The questionnaires were sent to the patients together with an accompanying letter and a stamped, addressed envelope. By including all eligible patients, the aim was to receive 100 completed and evaluable questionnaires per hospital. Questionnaires were sent to 200 patients from each hospital, 2 weeks after discharge. If no response was received after a further 2 weeks, a second questionnaire was sent with a reminder letter.

Final questionnaire

The final questionnaire was applied between September 2000 and January 2001 in six major hospitals in Switzerland

and Austria. The number of beds at each hospital ranged from 250 to 1480, and the number of anaesthetics per year from 5100 to 28 700. A total of 3785 questionnaires were sent to patients 1–2 weeks after discharge. The aim was to obtain at least 300 evaluable questionnaires from each hospital. Non-respondents were sent a second questionnaire 2 weeks later, together with a reminder letter.

The analysis of the construct validity and the creation of the dimensions with reliability analysis was repeated. Using standardized beta weights, we then calculated how great the relative influence of each of the dimensions was (importance).[11]

We also compared some perioperative characteristics (ASA class, extent of surgery, length of hospital stay, type of anaesthesia) of non-respondents to assess selection bias and representativeness.

Benchmarking

The comparison was based on the means of the total problem score and the two most frequently mentioned dimensions with problems ('Information/Involvement in decision-making' and 'Continuity of personal care by anaesthetist'). Possible effects of the following variables on the frequency of problems in each dimension were investigated: age, sex, state of health, length of hospital stay, extent of surgery, ASA class, type of health insurance, number of hospital stays in the past 6 months, type of anaesthesia, and level of education. If an influence was found, we investigated whether the composition of the patient sample from the hospitals ('case-mix') involved was the reason for the distortion of the benchmarking values. This made it possible to adjust the comparison between the individual hospitals for the confounding variables (i.e. to take into account effects caused by different composition of the patient samples). For the comparative analysis, the mean value over all hospitals (the total problem score and the scores for the two above-mentioned dimensions) were taken as reference. The hospitals were given letter codes A–F to preserve anonymity.

Statistical analysis

Pilot study: validity and reliability

The findings of the pilot study were first of all subject to a missing-value analysis in order to establish whether the questions or navigational instructions should be made more specific. Subsequent analysis of distributions was conducted in order to eliminate items with very skewed distributions. The content validity of the pilot instrument was further checked using a free-comment question asking for 'missing questions in the questionnaire' (Table 1). All individual questions that measured potential problems were dichotomized (i.e. were assigned to one of two groups depending on whether a problem was mentioned). For example, for the question: *Did you feel that you were adequately involved in the decision on the choice of anaesthesia?* The following answers were possible: yes – completely (not a problem response); yes – to a certain extent, and no (problem responses).

An individual global summed problem score was calculated on the basis of this problem rating (proportion of problems mentioned for all relevant questions). We checked for construct validity by establishing with multiple linear regression whether the single items had an influence on the different aspects of overall care (for example: *How would your rate the overall care you received for your anaesthesia?*) or on the global summed problem score. If an item was of low statistical importance, we had to decide whether to retain or exclude it, based on its content.

Creation of dimensions

We then created higher-level dimensions to categorize the patient's perception of quality on the basis of these individual problem ratings. To achieve this, we first of all subjected all problem indicators to exploratory factor analysis (principal component analysis, varimax rotation, scree test), to determine the number of dimensions that could be created from the problems mentioned.[12]

The internal consistency of the dimensions determined by factor analysis was then checked using reliability analysis. We calculated Cronbach's coefficient alpha.[7] [11] A score from 0 to 100 was then calculated for each dimension, which reflected the proportion of problem ratings in the respective area. The results of this analysis were discussed and the questionnaire was modified accordingly for the main survey.

Comparison of the hospitals and influence of potential confounding variables

The mean problem scores between the. hospitals were compared using analysis of variance and simple linear regression, with the total mean problem score as one reference and the best value as the second. The effects of the potential confounding variables on each dimension were first determined univariately, followed by multivariate analysis using multiple linear regression (forward-stepwise method). In the case of significant effects of these confounders, adjustment was performed. The findings are expressed in per cent (mean) or as mean (SD). Ranges are presented where appropriate. All analyses were conducted using the SPSS 10 analysis package (SPSS Inc. Chicago, IL, USA).

The multiple linear regression models, with and without adjustment for the confounding variables, are presented in the appendix.*

---

*The appendix is available to subscribers with the online version of the journal at the journal website.

Table 2 Results from focus groups

Anaesthetist	Must create an atmosphere of calm and give competent and comprehensive information and respond to the needs of the patient
Consultation before operation	Enough time, undisturbed atmosphere, discuss risks and put them into perspective, use language which is easy to understand; ideally the same person should perform the anaesthesia
Anxieties and fears	Not to wake up from anaesthesia, pain during surgery; side-effects of regional anaesthesia (paralysis)
On the day of the anaesthesia	Long waiting periods were felt to be very unpleasant (especially if no reasons are given)
During surgery	Regularly asking patients how they feel is important
Waking up from anaesthesia	Thirst, pain; rapid information on the outcome of surgery is important
Pain management	Involve the patient, patient-controlled analgesia is appreciated

Results

Focus groups

Table 2 summarizes the results from the focus groups.

Pilot questionnaire

The pilot questionnaire consisted of eight specific areas with a total of 53 questions. The areas were: before admission, patient information, day of anaesthesia, preparation for anaesthesia, during surgery (regional anaesthesia only), recovery room, return to the ward, and anaesthetist/nurse anaesthetist.

The overall response rate (including responses to reminder letters) was 61%. Ninety-three percent of respondents said the questionnaire was very easy or easy to complete, and 96% said it was very easy or easy to understand. Ninety percent of respondents completed the questionnaire within 20 minutes. Eighty-nine percent of respondents felt that all important questions related to anaesthesia had been asked, and 9% that some of them had been asked.

Pilot study

Missing-value analysis

Additional categories were incorporated into the final questionnaire, such as the possible response: *I underwent combined (regional and general) anaesthesia*, for the question on the type of anaesthesia.

Analysis of distribution

Some questions, particularly those that assessed overall satisfaction, showed very skewed distributions. The question '*Would you recommend the anaesthesiologist who looked after you to your family and friends?*' was excluded from the final questionnaire for this reason.

Only a few suggestions for missing questions were received, which supports the content validity of the pilot instrument. Additional questions suggested by patients therefore only resulted in minor modifications to the list of questions and were mainly related to the long-term after-effects of anaesthesia.

The analysis of construct validity using multiple linear regression of each individual aspect on the overall satisfaction was performed to establish the importance of individual aspects in the overall assessment. Since the questions on the overall impression (for example: *How would you rate the overall assessment of care you received for your anaesthesia*) were only of limited suitability because of their extremely skewed distributions (only 0.5–1.8% of all ratings were fair and poor), this analysis was primarily based on the global summed problem score. Taking into account the eight most important items, this resulted in an R^2 value of 0.85.

The factor and reliability analysis to enable grouping of the individual aspects into problem dimensions resulted in three scales with a Cronbach's alpha of >0.7 each ('Information/Involvement in decision-making/Continuity of personal care by anaesthetist'; 'Respect/confidence' and 'Delay management'), and two scales with a Cronbach's alpha <0.7 ('Pain management' and 'Nursing care in the recovery room').

Final questionnaire

A total of 2348 questionnaires from six hospitals were included in the analysis. The response rate was 62% (including responses to reminder letters) (range 53–69%). The age range of the respondents was 16–92 yr, and the female:male ratio was 51:49.

The analysis of the perioperative characteristics of the non-respondents showed that the type of anaesthesia and the extent of surgery had no influence on participation. The duration of the hospital stay (non-respondents had stays of 1 day less) and the ASA class (the patients in higher classes were slightly less prepared to participate) had a slightly positive effect on the readiness to participate amongst the respondents. Seen overall, any skew was minimal. The proportion of the declared variance in the readiness to participate was well below 0.5% in each case.

Creation and testing of dimensions

A total of 29 dichotomous problem ratings were included in the factor analysis. On the basis of the scree test,[12] a six-factor solution with an explained variance of 45.3% was selected as the best classification. The subsequent reliability analysis essentially confirmed the results of the factor analysis. The result showed that three of the dimensions had good internal consistency (Cronbach's alpha >0.7) and that two were of lower quality (Cronbach's alpha =0.43). The

Table 3 Number of items and internal consistency of each dimension (Cronbach's alpha); means (%) of the individual problem ratings per dimension, importance of the individual dimensions in the total score for problem ratings. *Only patients who were in the recovery room or could remember being there

Dimension	**No. of items**	**Cronbach's alpha**	**Mean problem score in %; (valid N)**	**Beta coefficient of total score (importance)**
Information/Involvement in decision-making	9	0.72	30.9 (2295)	0.60
Respect/Confidence	6	0.77	4.6 (2307)	0.26
Delays	4	0.75	7.2 (2185)	0.16
Nursing care in recovery room	2	0.69	1.9 (1506)*	0.07
Continuity of personal care by anaesthetist	4	0.43	32.2 (2324)	0.27
Pain management	4	0.43	9.3 (2162)	0.16
Total summed problem score	29	–	18.6	R^2=0.97

dimension 'Nursing care in the recovery room' consisted of only two items (Cronbach's alpha =0.69) (Table 3). It was then possible to calculate for each patient the problem scores for the six dimensions as a percentage of the problem ratings he or she gave.

Validity

In a multiple linear regression model, all six scores for the dimensions made a significant contribution (P<0.001) to the total summed problem score, which means that none of them was without importance in the total score. The analysis of the standardized beta weights (importance) showed that the dimension 'Information/Involvement in decision-making' had by far the greatest influence.

Table 4 shows the distribution of the potentially confounding variables in the six hospitals. Table 5 shows the results of the univariate and multivariate analysis of the confounding variables considered. The results of the multiple linear regression were as follows: (i) 'Information/ Involvement in decision-making' was by far the most important dimension, with a beta coefficient of 0.60.[1] Only the confounding variables subjective state of health (the worse the state of health, the more critical the patient) and type of anaesthesia (patients who underwent general anaesthesia were more critical) had an effect on the scores. (ii) 'Continuity of personal care by anaesthetist' (problem score: 32.6%; beta coefficient: 0.27) was influenced only by the factors age (the older the patient, the less critical), sex (men were less critical), and level of education (less criticism from those with lower level). (iii) Mean total problem score (problem score 18.6%) was influenced only by the factors age, sex, type of anaesthesia and subjective state of health (in accordance with the changes in the above-mentioned dimensions).

Figures 1–3 show the influence of the confounding variables that had effects on the above two dimensions and the total problem score, and compare these for the six hospitals. It can be seen, for example, that for hospital D, the non-adjusted values for 'Continuity of personal care by anaesthetist' were artificially elevated. This was because the average age of the patients at this hospital was lower (47.6 yr, as opposed to total mean of 52.7 yr); also, the level of education of the patients at this hospital was higher. Since both variables implied a more critical attitude, the raw values (non-adjusted) were artificially elevated. This means that hospital D was at a disadvantage in the benchmarking process as a result of its patient case-mix. Overall, the values for the problem scores for the two dimensions differed only slightly before and after adjustment, since the patients at the six hospitals were very similar with regard to the confounding variables (age, subjective state of health) or the differences between the confounding variables at the individual hospitals led to only slight changes in the average problem scores (sex, level of education, type of anaesthesia). Comparison of the raw and adjusted values for the total problem score showed—as for the two dimensions—an artificial elevation for hospital D (mainly because of the influence of age; adjusted values were not significantly above the total mean), and also an artificial lowering for hospital F (mainly influenced by subjective state of health; adjusted values were significantly higher than the total mean).

Discussion

The most important findings were as follows: (i) A psychometric questionnaire for the assessment of patient satisfaction with anaesthesia care must cover areas such as patient information and involvement in decision-making, contact with the anaesthetist, confidence, respect, and delay management. (ii) The most frequently mentioned problems from all hospitals were related to the dimension 'Information/Involvement in decision-making' (30.9%), and 'Continuity of personal care by anaesthetist' (32.2%). The values were lower than 10% for the other dimensions. (iii) By far the most important dimension was 'Information/ Involvement in decision-making'. (iv) The evaluation of patient satisfaction with anaesthesia care based on the analysis of individual dimensions (mean total problem score 18.6%) was clearly superior to the global summed rating (98.7% 'good' to 'excellent') in terms of method. (v) Relevant differences with regard to patient satisfaction with anaesthesia care were found between the hospitals. (vi) The effects of the confounding variables considered on the number of problems mentioned in the six hospitals were

Table 4 Distribution of potential confounding variables in the six hospitals (A–F). The first row for each variable contains numbers of patients, based on the information available. The remaining data are percentages. The category codes (1) to (5) represent the numeric coding for each variable used in the multiple linear regression

Confounding variable	**Category code**	**Hospital**						
		A	B	C	D	E	F	**Total**
Subjective state of health (*n*)		360	360	396	349	443	377	2285
	Excellent (1)	10.8	16.9	17.9	15.2	13.3	12.5	
	Very good (2)	32.8	38.1	32.6	36.1	28.7	31.8	
	Good (3)	41.9	35.0	35.1	33.8	39.5	37.7	
	Moderate (4)	12.8	9.7	11.6	12.9	17.2	14.6	
	Poor (5)	1.7	0.3	2.8	2.0	1.4	3.4	
	Mean	2.62	2.38	2.49	2.50	2.65	2.55	2.55
	SD	0.90	0.89	1.00	0.97	0.96	0.96	0.9
ASA class (*n*)		374	369	407	357	458	383	2348
	I (1)	25.9	44.1	57.2	42.3	41.5	34.5	
	II (2)	56.2	42.3	31.2	46.8	50.4	47.0	
	III (3)	17.4	13.3	11.1	10.9	8.1	18.0	
	IV (4)	0.5	0.3	0.5	0	0	0.5	
	Mean	1.93	1.70	1.55	1.69	1.67	1.85	1.72
	SD	0.67	0.70	0.71	0.62	0.72	0.69	0.69
Age (*n*)		363	357	391	345	439	369	2264
	Mean	55.4	54.1	50.6	47.6	53.5	55.0	52.7
	SD	17.7	17.1	17.9	17.1	16.3	17.6	17.4
Sex (*n*)		367	367	399	352	449	379	2313
	Female (1)	48.2	40.3	58.4	52.0	60.6	44.9	
	Male (2)	51.8	59.7	41.6	48.0	39.4	55.1	
Hospital stays in last 6 months (*n*)		355	330	366	327	422	346	2146
	1 (1)	66.2	77.9	68.9	70.3	66.8	62.7	
	>1 (2)	33.8	22.1	31.1	29.7	33.2	37.3	
Educational level (*n*)		355	347	384	341	447	368	2242
	Primary school/basic schooling (1)	16.9	14.4	18.5	11.4	15.9	20.9	
	Secondary school/comprehensive (2)	16.9	11.2	8.1	7.0	11.6	4.3	
	Vocational school (3)	42.3	53.0	46.9	49.0	44.5	49.5	
	High school (4)	10.7	10.4	20.1	19.9	20.1	12.8	
	Technical college/university (5)	13.2	11.0	6.5	12.6	7.8	12.5	
	Mean	2.86	2.92	2.88	3.15	2.92	2.92	2.94
	SD	1.21	1.11	1.13	1.10	1.12	1.23	1.15
Extent of surgery (*n*)		374	369	407	356	458	383	2347
	Minor (1)	8.0	8.4	13.8	5.9	10.5	12.8	
	Moderate (2)	60.2	74.3	66.8	71.6	66.4	62.1	
	Major (3)	31.8	17.3	19.4	22.5	23.1	25.1	
	Mean	2.24	2.09	2.06	2.17	2.13	2.12	2.13
	SD	0.59	0.50	0.57	0.51	0.57	0.60	0.56
Insurance (*n*)		365	364	388	347	444	379	2287
	Standard (1)	60.8	63.2	85.1	83.0	78.6	69.4	
	Semi-private/private (2)	39.2	36.8	14.9	17.0	21.4	30.6	
Duration of hospital stay (*n*)		374	369	405	354	458	383	2343
	Mean	8.4	8.3	7.6	7.6	8.1	7.1	7.8
	SD	7.0	6.3	7.4	7.8	6.9	7.4	7.15
Type of anaesthesia (*n*)		374	369	407	357	458	383	2348
	General (1)	70.9	73.7	71.0	94.7	75.3	63.2	
	Regional (2)	29.1	26.3	29.0	5.3	24.7	36.8	

only slight. In terms of method, however, despite the fact that the effects measured here were slight, evaluation and statistical analysis of the relevance of these variables is indispensable in ensuring that the benchmarking process is not distorted by case-mix.

Limitations of the study

We did not conduct a 'test-retest' procedure because we were of the opinion that it was too much to expect patients to complete a third, and possibly even a fourth, questionnaire,

Table 5 Analysis of the confounding variables considered. Statistical influence of all potential confounders was tested first at the univariate level (first line in each cell). All variables reaching a significance level of $P<0.20$ were entered simultaneously into a multivariate linear regression model. Method forward-stepwise with $P(\text{in})<0.05$ and P (out)<0.10 for the covariates, forced entry of the hospital-dummies. The significance of variables in the multivariate model (if appropriate) is shown in the second column for those variables Dim = dimension. $P<0.20$ (only bivariate), *$P<0.05$, **$P<0.01$; ***$P<0.001$, n.s, not significant

	Total score	Dim 1	Dim 2	Dim 3	Dim 4	Dim 5	Dim 6
Subjective state of health	*** ***	*** ***	*** ***	n s -	n s –	* –	*** ***
ASA class	**	n.s	**		*	***	n s
Age	*** ***	n.s –	*** ***	*** ***	** **	*** ***	** **
Sex	*** *	* –	–	–	n s –	*** ***	* –
Educational level	* –	n.s. –	n.s –	* –	* –	*** ***	n.s. –
Extent of surgery	n.s	n.s.	n.s.		n s		n s
Insurance	**	*	*	*	n s.		**
Duration of hospital stay	n s.			*	n s	***	n s.
Type of anaesthesia	*** **	*** ***	** *	* –	* –	** –	* *

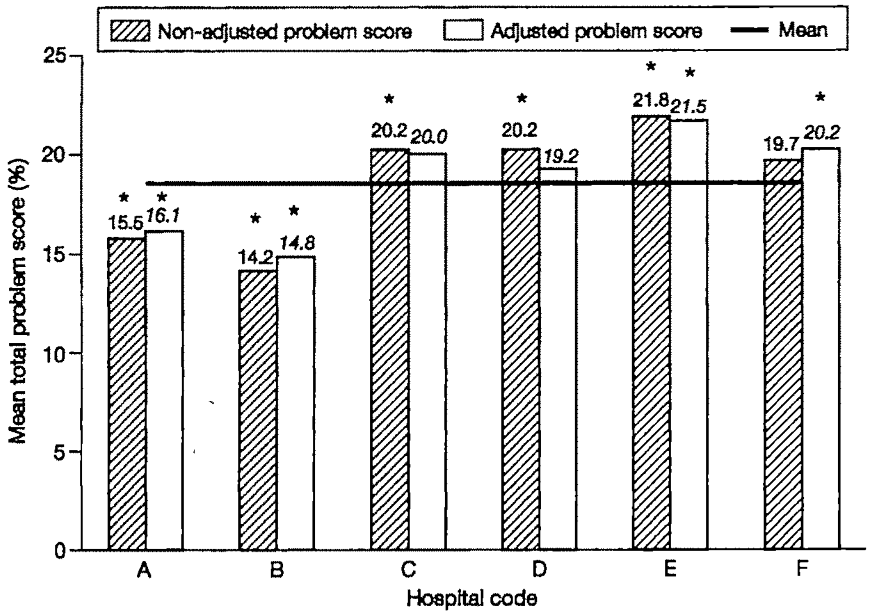


Fig 1 Comparison of the non-adjusted and adjusted mean total problem scores (%) at six hospitals (A–F). *$P<0.05$ *versus* total mean

and also felt that this would considerably increase the effort required in terms of practicability and cost. The value of retesting with regard to reliability is also controversial. It is generally accepted that, in order to obtain reliable results, the focus should be on internal consistency.[6]

Although we had some perioperative characteristics from the non-respondents, we did not have further important additional information from these patients. In their study, Fung and Cohen[13] also documented some personal details (age, sex, type of surgery), but did not state why the non-respondents did not reply. It would also be interesting to hear these patients' opinions on their degree of satisfaction with their anaesthesia care. Socio-medical investigations have shown that non-respondents may evaluate care less favourably than those who do respond.[14] In contrast, however, Ware and co-workers[15] found that patients who were more satisfied with their quality of care were less likely to return questionnaires.

Our response rate of 62% (n=2348) is lower than that achieved by Fung and Cohen (71%, n=45) and by Whitty and colleagues (73%, n=173).[16] This may be because our questionnaire was returned to an independent institute for evaluation.

It might be claimed that bias was introduced because two of the hospitals concerned participated in the pilot study, resulting in better scores in the main study. However, this is unlikely for the following reasons: first, different patients were surveyed in the pilot study and the final study; second, the two hospitals were not informed of the results of the pilot study, thus excluding the possibility of a shorter learning curve; third, there were only very slight differences between the overall problem scores for these two hospitals in the pilot study and the final study.

Although data do exist on predictors of postoperative outcome,[17–19] no findings are available on the influence of confounding variables on patient satisfaction.[5] [6] Our results

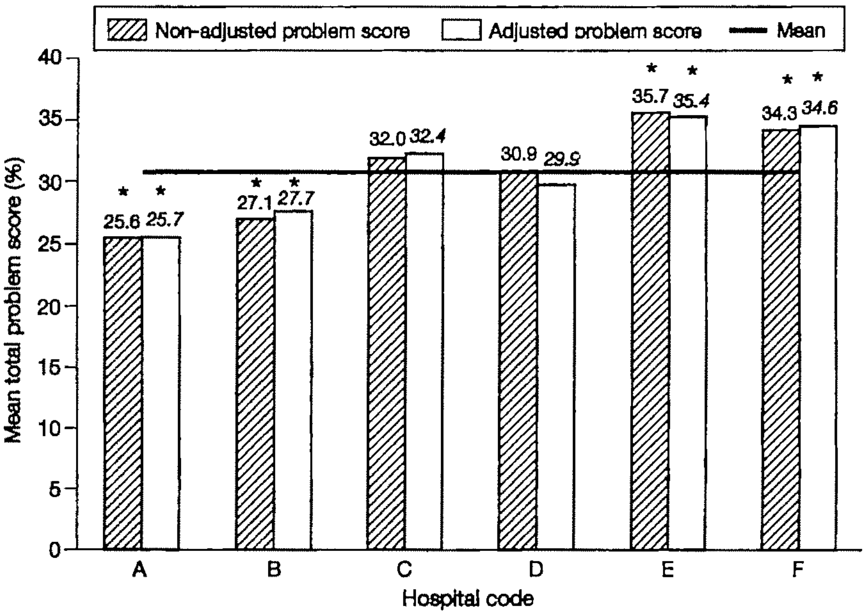


Fig 2 Comparison of the non-adjusted and adjusted mean problem scores (%) for the dimension 'Information/Involvement in decision-making' at six hospitals (A–F). *$P<0.05$ *versus* total mean.

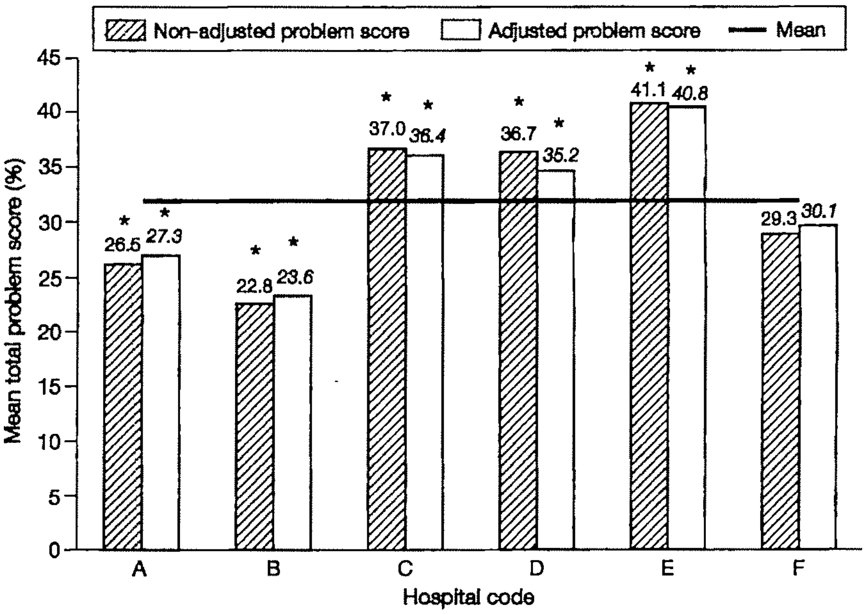


Fig 3 Comparison of the non-adjusted and adjusted mean problem scores (%) for the dimension 'Continuity of personal care by anaesthetist' at six hospitals (A–F). * $P<0.05$ *versus* total mean

showed that the subjective state of health, age, sex, level of education and type of anaesthesia had an effect on the dimensions 'Information/Involvement in decision-making' and 'Continuity of personal care by anaesthetist'. However, the extent of surgery, type of insurance, number of hospital stays in the past 6 months, duration of hospital stay and the ASA class had no influence on the number of problems mentioned. The variables selected may not be the most appropriate, since some of them were derived from outcomes research,[17] and we were only able to perform analyses with the confounding variables we selected.[20] We did not include, for example, social desirability as a confounding variable, as proposed by Le May and co-workers,[6] as the social desirability bias was minimized in our study by sending out questionnaires and not having interviewers present.[11]

Comparisons with results from other studies

Comparisons with other studies on patient satisfaction with anaesthesia care are difficult, since at present there is little or no similar published work in this area.[5 6] Moreover, current studies on patient satisfaction are of questionable value.[6 7 21]

The development of a psychometric questionnaire must follow a rigorous protocol.[5 7 11 12 22] For example, Sitzia[7] states that the prerequisites for a valid and reliable questionnaire are the presence of some elements of content validity *and* construct or criterion validity *and* reliability (internal consistency). According to Le May and co-workers[6] and Wu and co-workers,[21] none of the papers quoted by them followed such a rigorous protocol to measure patient satisfaction with general or regional anaesthesia in in-patients.

The generation of items must incorporate the patient's perspective by using focus groups, for example.[3 11 23 24] Otherwise, the surveys reflect the bias of the experts who constructed them. This is an instrument for content validity testing. Focus groups are required by several authors.[3 23 25] We found, however, only two publications on anaesthesia in which focus groups were used for item generation.[13 16] By using a pilot study including open questions, we also incorporated a second element of content testing.[7]

The statistical analysis of the patients' responses to the pilot questionnaire is an important part of the development of a psychometric questionnaire.[5] There is no consensus about the accepted level of reliability, but the most popular measure, the Cronbach coefficient alpha, should exceed at least 0.6 or 0.7.[26] Our results showed that the dimensions 'Information/Involvement in decision-making', 'Respect/Confidence' and 'Delay management' exceeded these levels (alpha >0.7). In agreement with others, we found that the dimension 'Information/Involvement in decision-making' was one of the areas where most problems were mentioned.[16 23 27]

In addition to the number of problems mentioned, the importance of the problems is also of great significance. As with reliability measurement, there are several methods available to assess this. The right answer is far from clear.[11] One of the accepted methods is weighting using multiple linear regression via beta weights.[11] In agreement with Fung and Cohen[13] who studied out-patients, our results showed that information (and communication) is the most important dimension. It is well recognized that involvement in decision-making improves patient satisfaction.[28]

It is also difficult to compare our results with those made at other hospitals because studies conducted so far have compared anaesthesia-related incidents and not patient satisfaction.[9] Measuring the quality of care by an anaesthesia team by comparing major outcomes has emerged as unsatisfactory because such events (in particular, death) occur only very rarely. Cohen and co-workers[10] concluded that their investigation of 25 000 patients in four hospitals was not powerful enough to demonstrate a difference in mortality. Because of the low incidence of major adverse outcomes, it is therefore very unreliable to use these as a basis to draw conclusions about the quality of an anaesthesia department.[10]

Unlike patient experience with hospital care,[29] as far as we are aware, there are no benchmarking studies on patient satisfaction with anaesthesia care conducted using a multidimensional, validated questionnaire. Analysis of patient surveys by Coulter and Cleary[23] also revealed problems with provision of information, respect for patients' preferences, and continuity of their care. Their findings also showed a striking difference between the total number of problems mentioned between the best and the worst hospitals.

The analysis of the confounding variables and the consequent adjustment based on the composition of the patient sample enabled us to compare the hospitals with each other. The effects found were very slight, however, because the hospitals were very similar with regard to the influence of the confounding variables considered. Such an analysis should nevertheless be conducted to elicit any possible effects and make appropriate adjustments.[10 30 31] It is known from the literature that older patients are less critical.[32] This was confirmed by our findings but other studies found no significant relationship of this sort.[25] In line with most other studies, our findings also showed a positive correlation between health status and satisfaction.[31]

In summary, the development of a psychometric questionnaire for the assessment of patient satisfaction with anaesthesia care requires the following of a rigorous protocol, including the patient's perspective. The implications for anaesthetic practice are that all hospitals involved should first of all consider how they can improve the situation with regard to the provision of information on anaesthesia care. As a continuous quality-improvement process, all measures taken should be evaluated and compared subsequently. The importance of communication —which can simply be used as a generic term for almost all our dimensions—cannot be emphasized strongly enough. 'Patients don't care what we know, they want to know that we care'.

Acknowledgements

This study was supported by the Department of Anaesthesiology, St Gallen Cantonal Hospital, Switzerland (financial support) and Picker Institute, Ibelweg 18a, CH-6300 Zug, Switzerland

References

1 Donabedian A. The quality of care: how can it be assessed? *JAMA* 1988; **260**: 1743–8

2 Ebner H, Kock CM. Qualitat als Wettbewerbsfaktor fur Gesundheitsorganisationen. In: Heimerl-Wagner P, Kock CM, eds. *Management in Gesundheitsorganisationen*. Wien: Ueberreuter, 1996; 72–101

3 Myles PS, Hunt JO, Nightingale CE, *et al.* Development and psychometric testing of a quality of recovery score after general anaesthesia and surgery in adults. *Anesth Analg* 1999; **88**: 83–90

4 Juran JM. *Juran on Quality by Design*, 1st Edn. New York: Free Press, 1992

5 Fung D, Cohen MM. Measuring patient satisfaction with anaesthesia care: a review of current methodology. *Anesth Analg* 1998; **87**: 1089–98

6 LeMay S, Hardy JF, Taillefer MC, Dupuis G. Patient satisfaction with anaesthesia services. *Can J Anaesth* 2001; **48**: 153–61

7 Sitzia J. How valid and reliable are patient satisfaction data? An analysis of 195 studies. *Int J Qual Health Care* 1999; **11**: 319–28

8 Myles PS, Williams DL, Hendrata M, Anderson H, Weeks AM. Patient satisfaction after anaesthesia and surgery: results of a prospective survey of 10 811 patients. *Br J Anaesth* 2000; **84**: 6–10

9 Bothner U, Georgieff M, Schwilk B. Building a large-scale perioperative anaesthesia outcome-tracking database: methodology, implementation, and experiences from one provider within the German quality project. *Br J Anaesth* 2000; **85**: 271–80

10 Cohen MM, Duncan PG, Pope WDB, *et al.* The Canadian four-centre study of anaesthetic outcomes: II. Can outcomes be used to assess the quality of anaesthesia care? *Can J Anaesth* 1992; **39**: 430–9

11 Streiner DL, Norman GR. *Health Measurement Scales. A Practical Guide to their Development and Use*, 2nd Edn. Oxford: Oxford University Press, 1995

12 De Vellis RF. *Scale Development. Theory and Applications*, 1st Edn. London. Sage Publications, 1991

13 Fung D, Cohen MM. What do outpatients value most in their anaesthesia care? *Can J Anaesth* 2001; **48**: 12–19

14 Ley P, Bradshaw PW, Kinsey JA, Atherton ST. Increasing patients' satisfaction with communication *Br J Soc Clin Psychol* 1976; **15**: 403–13

15 Ware JE, Snyder MK, Wright WR, Davies AR. Defining and measuring patient satisfaction with medical care. *Eval Program Plann* 1983; **6**: 247–63

16 Whitty PM, Shaw IH, Goodwin DR. Patient satisfaction with general anaesthesia. Too difficult to measure? *Anaesthesia* 1996; **51**: 327–32

17 Wolters U, Wolf T, Stutzer H, Schröder T. ASA classification and perioperative variables as predictors of postoperative outcome. *Br J Anaesth* 1996; **77**: 217–22

18 Duncan PG, Cohen MM. Anaesthetic morbidity: factors of significance to anaesthetic practice. *Can J Anaesth* 1987; **34**: 2–8

19 Farrow SC, Fowkes FG, Lunn JN, Robertson IB, Sweetnam P. Epidemiology in anaesthesia: a method for predicting hospital mortality. *Eur J Anaesthesiol* 1984; **1**: 77–84

20 Datta M. You cannot exclude the explanation you have not considered. *Lancet* 1993; **342**: 345–7

21 Wu CL, Naqibuddin M, Fleisher LA. Measurement of patient satisfaction as an outcome of regional anaesthesia and analgesia: a systematic review. *Reg Anesth Pain Med* 2001; **26**: 196–208

22 Crocker L, Algina J. *Introduction to Classical and Modern Test Theory*. Fort Worth: Harcourt Brace Jovanovic College Publishers, 1986

23 Allshouse KD. Treating patients as individuals. In: Gerteis M, Edgman-Levitan S, Daley J, Delbanco TL, eds. *Through the Patient's Eyes*. San Francisco: Jossey-Bass Publishers, 1993; 19–44

24 Dolan P, Cookson R, Ferguson B. Effect of discussion and deliberation on the public's views of priority setting in health care: focus group study. *Br Med J* 1999; **318**: 916–19

25 Cleary PD, McNeil BJ. Patient satisfaction as an indicator of quality of care. *Inquiry* 1988; **25**: 25–36

26 Malhotra NK. *Marketing Research – an Applied Orientation*, 2nd Edn. Upper Saddle River, NJ: Prentice Hall, 1996

27 Wisiak UV, Kröll W, List W. Communication during the preoperative visit. *Eur J Anaesthesiol* 1991; **51**: 327–32

28 Hornberger JC, Habraken H, Bloch DA. Minimum data needed on patient preferences for accurate, efficient medical decision making. *Med Care* 1995; **33**: 297–310

29 Coulter A, Cleary PD. Patients'experiences with hospital care in five countries. *Health Aff* 2001, **20**: 244–52

30 Greenfield S, Aronow H, Elashoff RM, Watanabe D. Flaws in mortality data. The hazards of ignoring comorbid disease. *JAMA* 1988; **260**: 2253–5

31 Aharony L, Strasser S. Patient satisfaction: what we know and what we still need to explore. *Med Care Rev* 1993; **50**: 49–79

32 Pascoe GC. Patient satisfaction in primary health care: a literature review and analysis. *Eval Program Plann* 1983; **6**: 185–210

British Journal of Anaesthesia **89** (6) 873–81 (2002)

Stress in UK intensive care unit doctors

S. Coomber[1] [6], C. Todd[2] [7]*, G. Park[1], P. Baxter[3], J. Firth-Cozens[4] [8] and S. Shore[5] [9]

[1]Addenbrooke's Hospital NHS Trust, Hills Road, Cambridge CB2 2QQ, UK. [2]Health Services Research Group, Department of Public Health and Primary Care, University of Cambridge, Institute of Public Health, Cambridge CB2 2SR, UK. [3]University of Cambridge Occupational Health Service, Fenner's, Gresham Road, Cambridge CB1 2ES, UK. [4]Department of Psychology, University of Leeds, Leeds, UK. [5]Centre for Applied Medical Statistics, Institute of Public Health, Robinson Way, Cambridge CB2 2SR, UK

[6]Present address: Ipswich Hospital NHS Trust, Heath Road, Ipswich IP4 5PD, UK.

[7]Present address: School of Nursing, Midwifery and Health Visiting, Coupland III Building, University of Manchester, Oxford Road, Manchester M13 9PL, UK.

[8]Present address: London Deanery, 20 Guilford Street, London WC1N 2BZ, UK.

[9]Present address: MRC Environmental Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton SO16 6YD, UK

**Corresponding author: School of Nursing, Midwifery and Health Visiting, The University of Manchester, Coupland III Building, Oxford Road, Manchester M13 9PL, UK. E-mail: chris.todd@man.ac.uk*

Background. Doctors have long been considered at risk of occupational stress.

Methods. A postal survey of all members of the Intensive Care Society using validated instruments.

Results. Eight-five per cent of members returned questionnaires and 70% were eligible for the study. Twenty-nine per cent were suffering General Health Questionnaire-12 (GHQ-12) identified distress and 12% Symptom Checklist-Depression (SCL-D) defined depression. There were no significant age or sex differences between staff suffering distress or depression and those who did not. Dissatisfaction with career correlated highly with both distress and depression ($P<0.01$). Twenty doctors (3%) were bothered by suicidal thoughts. The most stressful aspects of work were bed allocation, being over-stretched, effect of hours of work and stress on personal/family life, and compromising standards when resources are short. Logistic regression revealed mental health problems were predicted by five stressors: 'lack of recognition of one's own contribution by others'; 'too much responsibility at times'; 'effect of stress on personal/family life'; 'keeping up to date with knowledge'; and 'making the right decision alone'.

Conclusions. Nearly one in three ICU doctors appeared distressed (GHQ), and one in 10 depressed (SCL-D); this is no greater than that reported in other specialities. Perceived stressors reveal some key areas of concern for the employer and the specialty.

Br J Anaesth 2002; **89**: 873–81

Keywords: intensive care, depression; intensive care, occupational stress

Accepted for publication: July 19, 2002

Occupational stress is a recognized problem in health care workers, and doctors have long been considered to be at special risk.[1–4] Relatively few studies have been undertaken of UK hospital specialists, with six recent studies of consultants showing a range between 22 and 46% of respondents exhibiting clinically important levels of psychiatric morbidity, as assessed by standard psychiatric measures.[5–11] Figure 1 presents data from studies conducted by one of us that have used the General Health Questionnaire (GHQ) to assess psychiatric morbidity. It is clear that one in five to one in three doctors suffer from mental distress at any one time, depending on the threshold for morbidity accepted and the specialty in which they work. To study job stress within a single speciality, we undertook

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

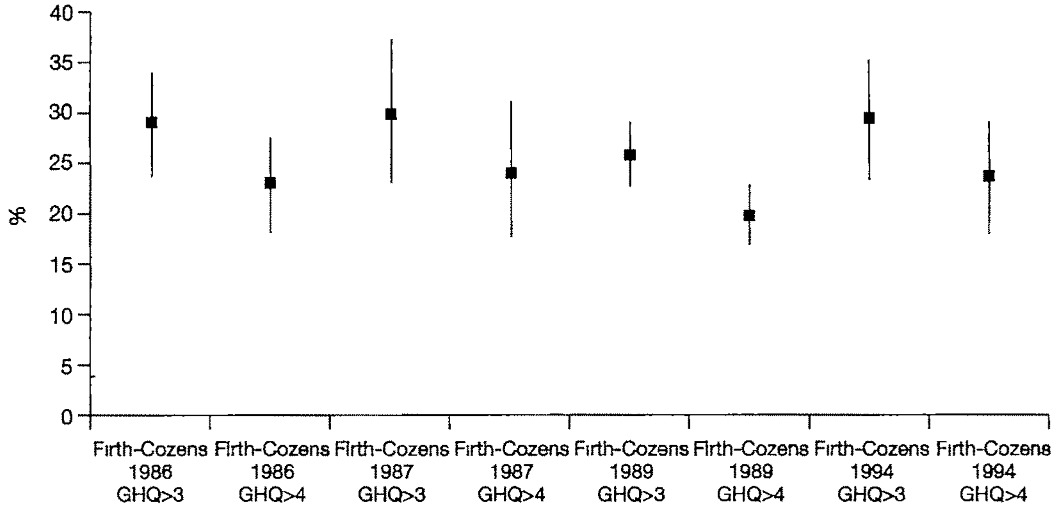


Fig 1 Percentage (95% CIs) of sample with GHQ scores indicative of mental distress in previous studies (morbidity thresholds of >3 and >4).

a national survey of intensive care specialists using the membership list of the Intensive Care Society (ICS) as a sampling frame. Intensivists routinely work in a demanding, highly technical environment where death and dying are common events,[12] and errors can be dangerous.[13] Limited resources affecting allocation of intensive care unit (ICU) beds can be a particular source of stress for ICU doctors.[14] In addition, many ICU consultants are trained or still practice in anaesthesia, a specialty suspected of being at a higher risk of stress-related ill-health,[15–18] and suicide[19 20] compared with other hospital doctors. The aim of the survey was to identify 'distressed' doctors as defined by the GHQ,[21] and relate this to repeated and long-term exposure to job stressors.

Methods

A complete list of ICS members working in ICUs in the UK was obtained. We sent a letter to each member explaining the study and asking him or her to take part. To maximize the response, a letter from the President of the UK ICS was enclosed, which emphasized the importance and confidentiality of the survey. Non-responders were followed-up with a maximum of two further mailings. The main questionnaire used was based on one validated in previous studies by one of us,[22–24] which included the 12-item GHQ,[21] and the Symptom Checklist Depression Sub-scale (SCL-D).[25] Information was also requested about workload, job satisfaction, and personal characteristics. Thus, all data in this paper are from validated screening instruments or based on self-report, using questions from previous studies. Questions were for the most part closed in nature.[26] For example, respondents were requested to indicate in a box how many hours they had worked during the previous week in total and then how many hours were engaged in NHS work, specific ICU work, on call time, teaching, etc. The frequency and severity of a list of ICU-specific stressors were rated using Likert type scales. Individuals indicated how frequently (scaled 0–2=never/occasional/often) and how stressful (scaled 0–4=not at all/slightly/moderately/very/extremely) they found each of the stressors. This list of stressors was based on those identified previously in surveys of junior doctors[27] and anaesthetists,[24] and adapted for the present study with the help of staff from Addenbrooke's Hospital NHS Trust, Cambridge.

The GHQ is a well-validated, self-administered questionnaire commonly used to detect psychiatric disorders in the community and other settings.[7 28] It focuses on two symptom categories: the inability to carry out normal functions and the appearance of new phenomena of a distressing nature.[21] It is known to detect both transient and sustained symptoms of distress. GHQ scores can be interpreted as an indicator of morbidity, and a threshold differentiates psychiatric 'cases' from 'non-cases'. We used two threshold scores; the 'standard' threshold of >3 and the 'high' threshold of >4, so that our data would be comparable with previous work.[22–24] The SCL-D was also scored in the standard way and a threshold of >1.5 used to distinguish depression 'cases'.[25]

As part of our study we asked about alcohol and drug use in a second separate questionnaire. Because of their sensitivity and so as to maximize response, these responses were anonymous and returned separately from the main questionnaire. Thus, we cannot link alcohol and drug use to specific responders.

Statistics

Data were double entered onto the computer. Parametric and non-parametric statistical analyses were undertaken using SPSS V.6.1. Throughout this paper, data reported are based on numbers of valid responses to items for each group or subgroup. Thus, numerators and denominators may not always total to the full sample size. To avoid products of

Table 1 Characteristics of survey responders (self report). Note in this and subsequent tables percentages are calculated on basis of valid responses to the item for each group or subgroup: two people did not report their sex

	Total	Male	Female	Director	Consultant	Junior
Number	627	523	102	144	389	94
	100%	83.4%	16.3%	23.0%	62.0%	15.0%
Age: mean	41.8	41.8	41.4	44.5	42.9	33.1
(SD)	(7.3)	(7.3)	(7.3)	(6.4)	(6.8)	(3.1)
Married or cohabiting	543	473	68	129	336	78
	86.6%	90.6%	66.7%	89.6%	86.6%	83.0%
Separated or divorced or widowed	25	20	5	7	16	2
	4.0%	3.8%	4.9%	4.9%	4.1%	2.1%
Single	58	29	29	8	36	14
	9.3%	5.6%	28.4%	5.6%	9.3%	14.9%
Partner is a doctor	155	115	40	31	97	27
	27.4%	23.6%	51.3%	23.3%	27.5%	32.9%

zero, we added a constant of one to frequency and stressfulness stressor scores when calculating products. Univariate analysis of personal characteristics and professional status was performed with the GHQ defined groups (using *t*-tests for those with two categories and ANOVA for three or more). Linear regression was performed with GHQ and SCL-D scores as dependent variables and age, sex, marital status, and each product of the individual stressors as independent variables. Forwards selection procedures were used to fit a multivariate model with a reduced number of variables and to identify predictors of GHQ and SCL-D defined morbidity. In the literature review, confidence intervals for estimates from other reports (Fig. 1) were calculated using Confidence Interval Analysis (CIA) Version 1.2.[29] We also used CIA in analysis of our anonymous alcohol and drugs questionnaire.

Results

Response rate

A total of 896 sets of questionnaires were sent out and 85% were returned (758/896). However, the ICS membership list used as the sampling frame included 108 (12%) doctors who replied that they were not currently working in ICU in the UK, and so we excluded them. Twenty-three questionnaires returned were inadequately completed to be included (i.e. indicated they did not wish to take part, or returned form blank). Thus, there were 627 eligible participants who had adequately completed the main questionnaire, giving a response rate of 70 (627/896), or 80% of potentially eligible responders (627/788). In addition, we had 643 anonymous alcohol and drugs questionnaires (643/788, 82% response) all of which were analysed.

Personal characteristics and professional status

Most respondents (533, 85%) were ICU directors and/or consultants (Table 1). Males predominated (523, 83%) in both senior and junior posts. The mean age of the participants was 41.8 yr, the youngest director being 34 yr, and the youngest consultant 30 yr. The majority (543, 87%) were married or cohabiting, about one in four with another doctor. Two thirds of females were married/cohabiting: half (37/68) with another doctor. Almost all the respondents (587, 94%) had trained in anaesthesia; the others were from general medicine, paediatrics, accident and emergency medicine, or surgery. Most worked in a general ICU (534, 85%), the remainder in cardiological or cardiothoracic ICU (36, 5.7%), neurology ICU (25, 4.0%), paediatric ICU (25, 4.0%), and a few in other specialized units. About half (331, 53%) worked in district general hospitals, and half in teaching hospitals (289, 46%), with the remainder in military or private hospitals (3, 0.5%). Four individuals did not state the type of hospital in which they worked.

Workload assessment

The respondents' jobs comprised a mean of 3.1 weekly ICU sessions (Table 2). A mean of 68.5 (SD 30.3) h were worked reportedly in the previous week, with a mean of 49.1 (16.9) h per week in the hospital. At home, the respondents reportedly worked a mean of 15.5 (22.2) NHS hours and 7.7 (14.7) non-NHS hours. Directors reported working a mean total of 64.3 (25.4) h and consultants 68.4 (32.5) h. Juniors reported the longest working week for the previous week, a mean of 77.8 (26.0) h.

The majority of respondents (505, 81%) were in full-time posts. Significantly more females (93/102, 91.2%) than males (412/517, 79.7%) worked in full-time posts (χ^2=7.48, df=1, P<0.01). Full-timers reported working a mean of 70.5 (30.9) h in total. Those in part-time posts reported working 61.0 (27.3) h which, although significantly less than full-timers (t=2.64, df=435, two-tailed P=0.009), was still high. Those who reportedly worked more than 30 'non-NHS hours' (23/627, 3.7%) were mostly full-time teaching hospital consultants, each responsible for five ICU sessions and 3.5–22 ICU beds. We interpret these 'non-NHS hours' to represent academic and/or private work, but this was not

Table 2 Workload indicators reported by responders. *Six not stated whether full or part time

	Total	Male	Female	Director	Consultant	Junior
Number	627	523	102	144	389	94
	100%	83.4%	16.3%	23.0%	62.0%	15.0%
Full-time post*	505	412	93	104	308	93
	80.5%	79.7%	91.2%	72.7%	80.0%	100%
Part-time post*	116	105	9	39	77	0
	18.5%	20.5%	8.8%	27.3%	20.0%	0%
Number of reported ICU sessions /week	3.1	3.2	2.7	3.9	2.6	3.8
(SD)	(2.0)	(2.1)	(1.7)	(2.1)	(1.6)	(3.0)
Mean total reported number of hours worked in previous week	68.5	69.5	63.7	64.3	68.4	77.8
(SD)	(30.3)	(30.1)	(31.4)	(25.4)	(32.5)	(26.0)
Mean reported NHS hours at work	49.1	49.0	49.6	46.6	47.3	61.0
(SD)	(16.9)	(16.1)	(20.5)	(12.8)	(16.7)	(18.6)
Mean reported number of ICU beds responsible for	7.3	7.5	6.5	7.2	7.0	8.9
(SD)	(3.8)	(3.9)	(3.0)	(3.7)	(3.6)	(4.5)
Mean reported number of non-ICU beds	6.3	6.5	4.8	5.9	6.0	7.6
(SD)	(7.7)	(8.3)	(3.5)	(6.0)	(6.5)	(12.5)

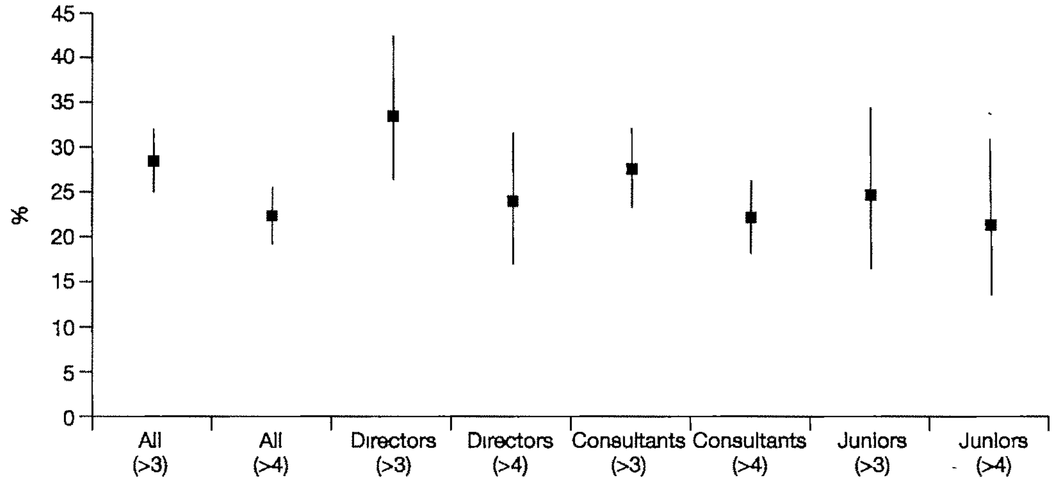


Fig 2 Percentage (95% CIs) of sample with GHQ scores indicative of mental distress in national sample of ICU doctors (morbidity thresholds of >3 and >4).

clear from the questionnaire. The respondents were responsible for a mean of 7.3 (3.8) ICU beds and 6.3 (7.7) non-ICU beds—mostly high dependency unit beds.

Psychiatric morbidity

For the GHQ, 174/610 (28.5%, 95% CI 24.9–32.1) survey respondents scored above the threshold score of three indicative of psychiatric morbidity (Fig. 2), and 136/610 (22%, 95% CI 19.0–25.6) scored above the more conservative threshold of four. On the SCL-D, 78 (12%, 95% CI 9.9–15.0) scored above the threshold score for depression of 1.5. There were no significant differences by post or sex for either scale (P>0.05, one-way ANOVA or two-tailed t-test) (Table 3). The most common symptoms of depression (highest mean scores for each symptom in the SCL-D) were 'feeling low in energy' (mean score 1.76) and 'worrying too much' (mean 1.50). Twenty doctors (3.2%, 95% CI 2.0–4.9) reported suicidal ideas ('thoughts of ending your life') 'moderately' to 'extremely' often in the past month. There was no significant difference in the frequency of these suicidal ideas between males and females (P>0.05). There was a moderate correlation between GHQ score and the 'thoughts of ending your life' SCL symptom score, particularly for males (males r=0.47, females r=0.43; P<0.001). No significant correlations existed between GHQ score and age, total hours worked in past week, or number of ICU beds. There was for males (but not for females) a weak correlation (r=0.14; P<0.01) between fear of making mistakes and 'thoughts of ending your life'.

Job satisfaction

Most respondents were reasonably satisfied with their choice of ICU as a career with 189 (30.4%) extremely satisfied. However, five respondents (0.8%) were extremely dissatisfied. Level of career satisfaction correlated with GHQ score (r=0.30, P<0.001) and depression (r=0.30, P<0.001).

Table 3 GHQ-12 and SCL-D score by post and sex (two consultants did not state their sex). Figures in italics are proportions stressed or depressed—expressed as percentage of the number of valid cases in each group or subgroup

	Number in each sub-group			**GHQ >3: 'stressed'**				**SCL >1.5: 'depressed'**			
	Director	**Consultant**	**Junior**	**Director**	**Consultant**	**Junior**	**Total**	**Director**	**Consultant**	**Junior**	**Total**
Male	122	322	79	43	81	20	144	15	34	12	61
				35.8%	*25.8%*	*26.7%*	*28.3%*	*12.3%*	*10.6%*	*15.2%*	*11.7*
Female	22	65	15	5	22	2	29	2	13	1	16
				22.7%	*35.5%*	*13.3%*	*29.3%*	*9.1%*	*20.0%*	*6.7%*	*15.7%*
Total	144	389*	94	48	104	22	174	17	48	13	78
				33.8%	*27.5%*	*24.4%*	*28.5%*	*11.8%*	*12.3%*	*13.8%*	*12.4%*

Table 4 Mean scores for all perceived stressors

Stressor	**How frequent (f) Mean**	**How stressful (s) Mean**	**Product (f+1)(s+1)**	
			Mean	**Standard deviation**
Bed allocation when ICU is full	1.59	2.40	4.08	2.50
Being over-stretched at times	1.46	2.27	3.52	2.24
Effect of hours of work on personal/family life	1.52	2.02	3.38	2.35
Talking to distressed relatives	1.60	1.46	2.45	1.75
Effect of stress on personal/family life	1.19	1.93	2.73	2.32
Compromising standards when resources are short	1.10	2.05	2.76	2.41
Treatment withdrawal	1.39	1.59	2.30	1.81
Keeping up to date with knowledge	1.51	1.41	2.24	1.91
Making the right decision *alone*	1.53	1.32	2.04	1.62
Dealing with death	1.58	1.25	2.01	1.47
Sleep deprivation	1.16	1.70	2.26	1.96
Fear of making mistakes	1.09	1.71	2.07	1.68
Difficult relations with senior colleagues	1.04	1.78	2.05	1.64
Overzealous/inappropriate treatment	1.06	1.69	1.97	1.59
Dealing with management *in general*	1.23	1.26	1.72	1.74
Making the right decision *as a team*	1.51	0.93	1.44	1.44
Lack of recognition of own contribution by others	1.01	1.31	1.75	1.97
Making time for research	0.96	1.25	1.65	2.00
Conflicts between ICU and theatre work	0.91	1.30	1.61	1.78
Dealing with *individual* managers	1.13	1.01	1.26	1.50
Difficult relations with nursing staff	0.85	1.20	1.25	1.27
Difficult relations with junior doctors	0.81	1.08	1.12	1.17
Lack of procedures for patient management	1.00	0.87	1.12	1.36
Having to do menial or repetitive tasks	0.96	0.78	1.00	1.53
Too much responsibility	0.63	1.05	1.14	1.55
Commitments to private practice	0.68	0.76	0.82	1.21
Managing ICU budgets	0.58	0.76	0.87	1.50
Feeling under-utilized	0.44	0.57	0.55	1.22
Threat of violence	0.16	0.45	0.29	0.82
Sexual harassment	0.08	0.17	0.10	0.56

Analysis of individual stressors

An impression of the relative day-to-day perceived importance of each stressor can be represented by the mean product of frequency (f) times stressfulness (s) (i.e. mean ($f \times s$)). But to avoid zero products we calculate (f+1)(s+1) (Table 4). The stressor 'bed allocation when ICU is full' scores highly: it is the *most stressful* factor of all (s=2.40), and reportedly occurs *often* (f=1.59). At the other end of the spectrum, this group of predominantly male doctors report that sexual harassment is both infrequent (0.08) and not stressful when it occurs (0.17). Talking to distressed relatives' is the *most frequent* stressor (f=1.60) but only considered slightly-to-moderately stressful (s=1.46). Similarly, 'dealing with death' is perceived as a frequent event (f=1.58) but is not especially stressful (s=1.25). 'Being over-stretched at times' is also frequently reported (f=1.46), with the second highest score for stressfulness (s=2.27). In contrast, 'feeling under-utilized' is relatively rare (f=0.44) and has low reported stressfulness (s=0.57).

As a stressor, 'making the right decision *alone*' occurs as often as 'making the right decision *as a team*' (f=1.53 and 1.51, respectively), but it appears to be more stressful to do so alone (s=1.32 compared with 0.93). 'Fear of making mistakes', 'difficult relations with senior colleagues', 'sleep deprivation', and 'overzealous/inappropriate treatment' are

Table 5 Main stressors for distressed doctors (linear regression model) (GHQ score)

Stressor	**Regression coefficient (B)**	**95% Confidence intervals**	***P* value**
Constant	6.819		
Effects of stress on personal/ family life	0.472	(0.354, 0.589)	<0.0001
Too much responsibility at times	0.340	(0.197, 0.482)	<0.0001
Lack of recognition of one's own contribution by others	0.298	(0.168, 0.429)	<0.0001
Sexual harassment	−0.268	(−0.578, 0.004)	0.092

Table 6 Main stressors for depressed doctors (linear regression model) (SCL-D score)

Stressor	**Regression coefficient (B)**	**95% Confidence intervals**	***P* value**
Constant	−0.335		
Effects of stress on personal/ family life	0.068	(0.054, 0.081)	<0.0001
Lack of recognition of one's own contribution by others	0.038	(0.023, 0.053)	<0.0001
Making the right decision alone	0.028	(0.009, 0.046)	0.0040
Keeping up to date with knowledge	0.026	(0.011, 0.042)	0.0012
Too much responsibility at times	0.025	(0.008, 0.041)	0.0037

each perceived to be stressful when they occur (respectively, s=1.71, 1.78, 1.70, and 1.69), but are only occasional events (f=1.09, 1.04, 1.16, and 1.06).

'Effect of hours *of work* on personal/family life' appears to be slightly greater than the 'effect of *stress* on family/ personal life', and occurs more frequently (f=1.52 and 1.19), although both are stressful (s=2.02 and 1.93).

Predictors of morbidity

In the multivariate model, three variables (Table 5) were highly significant in predicting GHQ score; 'effects of stress on personal/family life', 'too much responsibility at times', and 'lack of recognition of one's own contribution by others'. All of them were important stressors, but not those expected from Table 4. Similarly, linear regression analysis with SCL-D depression score as the dependent variable (Table 6) showed the same three variables as highly significant plus 'making the right decision alone' and 'keeping up to date with knowledge'.

Use of alcohol and drugs

Nearly one in five (18%, 95% CI 14.8–20.7) (114/643) reported 'many irregular' or 'many regular' drinks, but most (53%, 95% CI 48.9–56.6) (339/643) were 'few regular' drinkers and just 24 responders (4%, 95% CI 2.4–5.5) were abstinent. Some 14% (95% CI 11.0–16.3) (88/643) smoked and 5% (95% CI 3.2–6.6) (30/643) reportedly smoked and drank heavily. Twelve per cent reported taking drugs to help them sleep (95% CI 9.0–14.0) (74/643), 4% took antidepressants (95% CI 2.9–6.2) (28/643), and 4% anxiolytics (95% CI 2.3–5.3) (23/643). Whilst about half of drugs used to aid sleep were self-prescribed (55%, 95% CI 43.4–67.0) (41/74), most antidepressants were prescribed by another doctor (75%, 95% CI 55.1–89.3) (21/28). In addition, 5% (95% CI 3.3–6.8) (31/643) reported use or past use of drugs such as cannabis for relaxation or recreation.

Discussion

The satisfactory response rate probably reflects both the suitability of the study design, and the doctors' interest in the topic. It compares favourably with previous studies[7–9 11 30 31] which had response rates between 72 and 80%. The high response rate in this national group gives us confidence that the data are representative. There are, however, two possible sources of selection bias. First, ICS membership may not be entirely representative of the target population of UK intensive care doctors, but we could not identify any other realistically usable source of data to check on this. Second, the responders may not represent the whole ICS membership in terms of psychiatric morbidity, but we had no way of confirming the state of mental health of the non-responders. Nonetheless, we would argue that the level of morbidity we have detected is likely to be a conservative estimate, as it can be argued that non-response is associated with 'burn out' and 'stress'. However, we do recognize that such conjecture needs further investigation, as non-response may be simple disinterest rather than overwork and lack of time.

Our main findings in this national survey of intensive care specialists were that nearly one in three (29%) showed evidence of psychiatric morbidity as identified by the GHQ-12. Some 12% showed clinically important levels of depression identified by the SCL-D. Some 3% reported having suicidal thoughts moderately or extremely often in the previous month, and suicidal ideation correlated with GHQ scores. The doctors' GHQ and SCL scores showed no relation with age, reported hours worked in the previous week, nor the number of ICU beds for which they were responsible. This lack of association with hours of work has been noted in other studies.[23 24 30 31] Although we asked about hours worked, not hours slept in the previous week, sleep deprivation was perceived as an occasional and important stressor. Nonetheless, these doctors reportedly worked long hours, clearly in excess of the subsequently introduced Working Time Regulations,[32] an issue in itself of some concern.

Our anonymous alcohol and drugs questionnaire revealed quite high levels of alcohol (mis)use and indication of other substance (mis)use. However, we cannot make a great deal of these data as numbers are relatively small and for methodological and confidentiality reasons we cannot link them to the data from our main datasets. They do, however, suggest that there may be number of maladaptive 'coping' strategies in use by these doctors.

Job satisfaction has been suggested previously to be protective against burnout,[8] and we found that dissatisfaction with choice of ICU career correlated significantly with both GHQ and SCL scores. The five most frequent and most stressful factors reported were: bed allocation when ICU is full; being over-stretched at times; effect of hours of work on personal/family life; effect of stress on personal/family life; and compromising standards when resources are short. At first sight, all of these stressors seem to be integral to the work of an ICU doctor, and are related to levels of resource for an ICU. Use of paired stressors in the list show that 'personal/family life' is reported to be more affected by 'hours of work' than by 'stress' *per se*, although both are seen as important. Further down the list, 'making the right decision *alone*' is reported to be more stressful than 'making the decision *as a team*'. The benefits of teamwork on stress levels are well reported elsewhere.[3] However, further statistical analysis showed that a different range of stressors predicted psychiatric morbidity (i.e. GHQ and SCL scores): lack of recognition of one's own contribution by others; too much responsibility at times; effects of stress on personal/family life; keeping up to date with knowledge; and making the right decision *alone*. This list is not so much a reflection of resource issues, but may be more related to the responsibilities of ICU doctors and the perceived reputation of the specialty. If these are the stressors of the distressed and depressed doctors, then addressing them is likely to have a greater impact on doctors' well being than purely focusing on allocation of resources.

The SCL depression sub-scale has also been used by Firth-Cozens, in studies of a cohort of doctors followed since medical school.[22 23] Ten years after qualifying, some 18% of those doctors scored above the clinical threshold for depression,[30] but only 12% of ICU doctors were depressed. The confidence intervals for the proportion of ICU doctors expressing suicidal ideas (3.2%: 95% CI 2.0–4.9) overlap with other studies; of junior doctors[23] (5.9%, 95% CI 2.9–10.6) and of anaesthetists[11] (12.2%, 95% CI 4.1–26.2), suggesting they do not differ. Thus, the levels of stress reported here are not very different from those observed in previous studies (Figs 1 and 2), and certainly less than the 44% recently reported for accident and emergency doctors.[33] Our findings compare with findings amongst anaesthetists, whose major stressors were effects of work on personal life, overwork, making mistakes, and making decisions.[24] Apart from worry about making mistakes, the ICU doctors (who are mostly from an anaesthetic background) rated similar stressors highly. The findings that number of hours worked and number of beds the doctor is responsible for relate to morbidity have been noted before.[3 34] The lack of sex difference in GHQ scores has also been reported elsewhere.[23] We cannot, of course, infer causality in any relationship between occupational stressors and mental health. The more depressed or distressed doctor may well give greater weighting to his or her stressors, and feel more dissatisfied with choice of career. Previous surveys of medical students and hospital doctors using the GHQ-12[5 8 22 23] have also shown high percentages (26–30%) of doctors scoring above a GHQ-12 threshold of 3 (Fig. 1). Surveys using GHQ-28[7 11] have shown 21–46% scoring above the GHQ-28 threshold of >5 for psychiatric morbidity.

Doctors, it seems, have more problems than the average British worker (17.8% for the 1995 Household Panel Survey; www.irc.essex.ac.uk/bhps).[35] However, some authors dispute that stress and mental health problems in health care workers are any higher than the general population, and ascribe raised stress levels to questionnaire bias, especially in doctors.[36 37] Such an explanation, however, does not easily account for differences within the medical profession as a whole.

Whilst anecdotally, ICU is a high-stress speciality, it seems that measuring distress alone may be missing the point, as our regression modelling revealed. The level of mental health problems we found is not apparently related to the ICU doctors' characteristics, nor to the type of unit, nor long hours of work. Feeling that the responsibility is too great, lack of peer recognition, worry about compromising standards, effects of stress on home life, distressed relatives, and the pressure to keep up to date are clearly issues in need of resolution. We may need to develop teamwork to modify these stressors,[3] but we must recognize that this also implies a need for resources to develop teams.

At an average age of 42 yr these doctors have another 20 yr or so of professional life ahead. Over a prolonged period, stress could lead to increased risk of health problems, both mental and physical. Consideration needs to be given to what aspects of the occupational stressors are amenable to change, and what practical steps, if any, can be taken to identify and support vulnerable individuals at an early stage. It is logical to address factors which may contribute to attrition rates of consultants, as they are expensive to train (£232 000) and each lost working year of a consultant costs the NHS £30 000 in terms of annuitized training costs over his or her expected working life.[38] A rational strategy for the NHS would be to provide employment environments in which doctors can practice effectively without compromising their own health.

Strategies to reduce harmful effects on doctors' health should include reduction of frequency and intensity of identified stressors, early detection of problems and maladaptive coping (e.g. alcohol or drug use), and effective medical treatment and rehabilitation of the sick doctor. The principles of management of stress in healthcare workers in general apply to ICU. However, reducing stressors in ICU may in practice be difficult. In the meantime, individual distressed doctors need to have improved access to services, such as the BMA Stress Counselling Service,[39] and the National Counselling Service for Sick Doctors (www.ncssd.org.uk). Prevention, in the form of stress management has begun in some trusts already,[40] and is worthy of future development.

Acknowledgements

We thank the ICS for their help with supporting the study throughout. Our thanks to the doctors who gave their time to complete our questionnaire, to Julian Lipscombe for his help with data preparation, to Brian Thom who assisted Sarah Shore with the regression analysis and to Malcolm Campbell for further data checking and analysis. Thanks are also due to Prof Sydney Brandon for his encouragement and helpful comments on this paper prior to his death. Funding: the Intensive Care Society, the John Farman Intensive Care Unit and the Occupational Health Department, Addenbrooke's Hospital NHS Trust all helped to fund the survey. Dr Todd's post was funded by NHS Eastern Region R&D

References

1 Robins S, Cooper CL, Mayers W. *Stress and the Medical Profession*. London: BMA, 1992

2 Smith R. All doctors are problem doctors. *Br Med J* 1997; **314**: 841–2

3 Firth-Cozens J. Hours, sleep, teamwork and stress. *Br Med J* 1998; **317**: 1335–6

4 Berger A. Surviving (and even enjoying) medicine. *Br Med J* Classified, 29 April 2000; 2–3

5 Borrill CS, Wall TD, West MA, et *al Mental Health of the Workforce in NHS Trusts*. Phase 1. Final report. March, 1996

6 Kapur N, Borrill C, Stride C. Psychological morbidity and job satisfaction in hospital consultants and junior doctors: a multicentre cross-sectional survey. *Br Med J* 1999; **317**: 511–12

7 Caplan RP. Stress, anxiety and depression in hospital consultants, general practitioners and senior health service managers. *Br Med J* 1994; **309**: 1261–3

8 Ramirez AJ, Graham J, Richards MA, Cull A, Gregory WM. Mental health of hospital consultants. the effects of stress and satisfaction at work. *Lancet* 1996; **347**: 724–8

9 Heyworth J, Whitley TW, Allison EJ jr, Revicki DA. Correlates of work-related stress among consultants and senior registrars in accident and emergency medicine. *Arch Emerg Med* 1993; **10**: 271–8

10 Agius RM, Blenkin H, Deary IJ, Zealley HE, Wood RA. Survey of perceived stress and work demands of consultant doctors. *Occup Environ Med* 1996; **53**: 217–24

11 Blenkin H, Deary IJ, Wood RA, Zeally HE, Agius RM. Stress in NHS consultants. *Br Med J* 1995; **310**: 534

12 Ryan DW. Providing intensive care. *Br Med J* 1996; **312**: 654

13 Abramson NS, Wald KS, Grenvik ANA, Robinson D, Snyder JV. Adverse occurrences in Intensive Care Units. *JAMA* 0000; **244**: 1582–4

14 Carnall D. UK reviews intensive care and emergency services. *Br Med J* 1996; **312**: 655

15 McNamee R, Keen RI, Corkhill CM. Morbidity and early retirement among anaesthetists and other specialists. *Anaesthesia* 1987; **42**: 133–40

16 Redfern N. Morbidity among anaesthetists. *Br J Hosp Med* 1990; **43**: 377–81

17 Milner QJW, Zeigler ESM. Early death amongst anaesthetists. *Anaesthesia* 1997; **52**: 797–8

18 Seeley HF. The practice of anaesthesia—a stressor for the middle-aged? *Anaesthesia* 1996; **51**: 571–4

19 Neil HA, Fairer JG, Coleman MP, Thurston A, Vessey MP. Mortality among male anaesthetists in the UK. *Br Med J* 1987; **295**: 360–2

20 Helliwell PJ. Suicide amongst anaesthetists-in-training. *Anaesthesia* 1983; **38**: 1097

21 Goldberg D, Williams P. *A User's Guide to the General Health Questionnaire*, 1st Edn. Windsor: NFER-NELSON Publishing, 1988

22 Firth-Cozens J. Levels and sources of stress in medical students *Br Med J* 1986; **292**: 1177–80

23 Firth-Cozens J. Emotional distress in junior house officers. *Br Med J* 1987; **295**: 533–6

24 Firth-Cozens J. *Levels and Sources of Stress in Anaesthetists*. Report to Association of Anaesthesists of Great Britain and Ireland. London: Association of Anaesthetists of Great Britain and Ireland, 1989.

25 Derogatis LR, Lipman RS, Covi MD. SCL-90: an outpatient psychiatric scale—preliminary report. *Psychopharm Bull* 1973; **9**: 13–20

26 Fowler FJ. *Survey Research Methods*. London: Sage, 1993

27 Firth-Cozens J. Morrison LA, Sources of stress and ways of coping in junior house officers. *Stress Med* 1989; **5**: 121–6

28 Banks MH, Clegg CW, Jackson PR, Kemp JN, Stafford EM, Wall TD. The use of the general health questionnaire as an indicator of mental health in occupational settings. *J Occup Psychol* 1980, **53**: 187–94.

29 Gardner MJ, Gardner SB, Winter PD. Confidence Interval Analysis Microcomputer Program Version 1.2. BMJ Publishing Group, 1992.

30 Firth-Cozens J. Predicting stress in general practitioners: 10-year follow-up postal survey. *Br Med J* 1997; **315**: 34–5

31 Firth-Cozens J. Individual and organisational predictors of depression in general practitioners. *Br J Gen Pract* 1998; **48**: 1647–51

32 Byers S, The Secretary of State for Trade and Industry. *Working Time Regulations* 1999: Statutory Instrument No. 3372. London: HMSO Publications, 1999

33 Burbeck R, Coomber S, Robinson S, Todd C. Occupational stress in consultants in accident and emergency medicine: a national survey of levels of stress at work. *Emerg Med J* 2002; **19**: 234–8

34 Goodfellow A, Varnham R, Rees D, Shelley MP. Staff stress on the intensive care unit: a comparison of doctors and nurses. *Anaesthesia* 1997; **52**: 1037–41

35 British Household Panel Survey 1993–4. *British Household Panel*

Survey, UK Data Archive Colchester: Institute for Social and Economic Research, 2001

36 Weinberg A, Creed F. Stress and psychiatric disorder in healthcare professionals and hospital staff. *Lancet* 2000; **355**: 533–7

37 McManus IC, Winder BC, Gordon D. Are UK doctors particularly stressed? *Lancet* 1999; **354**: 1358–9

38 Netten A, Knight J, Dennett J, Cooley R, Slight A. *A 'Ready Reckoner' for Staff Costs in the NHS*. Canterbury: Personal Social Services Research Unit, Vol. 1, 2000

39 BMA Stress Counselling Service (analysis of nearly 800 calls made between 9 April launch and 21 June) *BMJ News* 1996; 6 July; 313

40 Davies RH. Junior doctors and stress. *Lancet* 1998; **352**: 1780

British Journal of Anaesthesia 89 (6). 882–7 (2002)

BJA

LABORATORY INVESTIGATIONS

Comparison of effects of anandamide at recombinant and endogenous rat vanilloid receptors

J. C. Jerman[1]*, J. Gray[2], S. J. Brough[1], L. Ooi[2], D. Owen[2], J. B. Davis[2] and D. Smart[2]

[1]Department of Discovery Research and [2]Department of Neurology, GlaxoSmithKline, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK

**Corresponding author. E-mail: jeff_jerman@gsk.com*

Background. Anandamide, an endogenous lipid, activates both cannabinoid (CB_1) and vanilloid (VR1) receptors, both of which are co-expressed in rat dorsal root ganglion (DRG) cells. Activation of either receptor results in analgesia but the relative contribution of CB_1 and VR1 in anandamide-induced analgesia remains controversial. Here we compare the *in vitro* pharmacology of recombinant and endogenous VR1 receptors using calcium imaging, in clonal and DRG cells, respectively. We also consider the contribution of CB_1 and VR1 receptors to anandamide-induced analgesia.

Methods. Using a Flurometric Imaging Plate Reader (FLIPR™), calcium imaging has been used to study the effects of several vanilloid and cannabinoid ligands in rat VR1-transfected HEK293 (rVR1-HEK) cells and in DRG cells. The effect of pre-exposure of several vanilloid and cannabinoids has also been compared in DRG cells.

Results. The VR1 agonists capsaicin, olvanil, (*N*-(4-hydroxyphenyl-arachinoylamide) (AM404) and anandamide caused a concentration-dependent increase in intracellular calcium concentration ($[Ca^{2+}]_i$), with similar temporal profiles in both rVR1-HEK and DRG cells, and potency (pEC_{50}) values of 8.25 (SEM 0.11), 8.37 (0.04), 6.96 (0.06), 5.85 (0.01) and 7.45 (0.10), 7.55 (0.07), 6.10 (0.13), approximately 5.5, respectively. These responses were inhibited by the VR1 antagonist capsazepine (1 μM). In contrast, application of synthetic cannabinoid antagonists failed to inhibit the anandamide-induced increase in $[Ca^{2+}]_i$. Reapplication of VR1 agonists significantly inhibited a subsequent challenge to either capsaicin or anandamide in either cell type, whilst pre-exposure to cannabinoid agonists were without effect.

Conclusion. Here we provide evidence that the pharmacology of recombinant rVR1 receptors is similar to those endogenously expressed in DRG cells. Moreover, we have shown that VR1, but not CB_1, receptors are involved in anandamide-induced responses in dorsal root primary neurones *in vitro*. Therefore, the analgesic properties of anandamide are likely to be mediated, at least in part, by VR1 activation in DRG cells *in vivo*.

Br J Anaesth 2002; **89**: 882–7

Keywords: analgesics non-opioid, anandamide; spinal cord, dorsal root ganglion; equipment, flurometric imaging plate reader; receptors, cannabinoid; receptors, vanilloid

Accepted for publication: July 29, 2002

The development of novel therapeutics, efficacious in the clinical control of pain but lacking undesirable side-effects, has thus far proved elusive, despite a considerable research effort. The identification of two distinct cannabinoid receptor subtypes,[1 2] termed CB_1 and CB_2, and cloning of these cannabinoid receptors,[3] has facilitated extensive study of their pharmacology and distribution.[3] Soon after the cloning of CB_1 and CB_2 receptors, which are members of the G-protein-coupled receptor superfamily and couple specifically to $G_{i/o}$ G-proteins, two endogenous lipid

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

activators, anandamide and 2-arachidonylglycerol (2-AG), were identified in mammalian tissues.[4–6] Several lines of investigation have led workers to conclude that the typical *in vivo* actions of cannabinoids—that are analgesia, effects on appetite, mood, hypotension, cognition, spontaneous activity and thermoregulation—are exclusively CB_1 receptor-mediated.[3] However, studies using selective CB_1 receptor antagonists[7] and mice lacking the CB_1 gene[8] provide compelling evidence against CB_1 receptors being solely responsible for the *in vivo* actions of anandamide. This raises the question of how anandamide exerts non-CB_1 receptor-mediated effects, such as analgesia?

The vanilloid receptor (VR1) is a ligand-gated ion channel expressed on sensory neurones and plays an important role in nociception.[9] Prolonged activation of VR1 results in receptor desensitization and analgesia[9] and it has recently been reported that anandamide is an agonist at VR1 receptors.[10 11] However, it is difficult, and often misleading, to correlate results derived from *in vitro* assay systems, using recombinant receptors[10], with those from isolated tissue preparations,[11] especially when trying to model the situation *in vivo*.

Therefore, in the present study we have used a fluroimetric imaging plate reader (FLIPR™) to measure changes in intracellular calcium concentration ($[Ca^{2+}]_i$) and compared the effects of anandamide at recombinant VR1 receptors with those in physiologically relevant dorsal root ganglion (DRG) primary cell cultures.

Materials and methods

Cloning and expression of rat VR1

Cloning and expression of rat VR1 (rVR1) was performed as described previously.[12] In brief, a rat mammalian expression construct was generated by amplification of cDNA from reverse transcribed adult DRG mRNA, using forward and reverse primers incorporating the restriction sites RVR1F-*Hind*III and RVR1R-*Xba*I. Reaction products were cloned into $pBSSKII^+$ (Stratagene) and subcloned into the *Hind*III–*Xba*I sites of pcDNA3.1 (Invitrogen). Adherent human embryonic kidney (HEK293) cells were then transfected with rVR1.pcDNA3.1 using Lipofectamine Plus (Life Technologies) and stable clones generated following application of selection media (genetecin, 400 μg ml^{-1}) and colony cloning.

Cell culture

HEK293 cells stably expressing the recombinant rVR1 receptor, were maintained in culture in minimum essential medium (MEM) supplemented with non-essential amino acids, 10% fetal calf serum and 2 mM L-glutamine. Cells were grown as monolayers under 95:5% air:CO_2 at 37°C and passaged every 3–4 days. The highest passage used was 20. Dissociated rat neonatal DRG cultures were prepared as described by Skaper and co-workers.[13] In brief, DRG cells were prepared from 8-day-old Sprague–Dawley rats and cultured in microtitre plates in DMEM containing N2 supplements, β-NGF (50 ng ml^{-1}), bovine serum albumin (BSA) (0.05%), penicillin (100 units ml^{-1}) and streptomycin (100 units ml^{-1}). Cells were cultured for 3 days and maintained under 95:5% air:CO_2 at 37°C.

Measurement of $[Ca^{2+}]_i$ using the FLIPR™

rVR1-HEK cells were seeded into black walled clear-base 96-well plates (Costar, UK) at a density of 25 000 cells per well in MEM, supplemented as above and cultured overnight. Cells were then incubated with the cytoplasmic calcium indicator, Fluo-3 in the acetoxylmethyl ester form (4 μM; Teflabs, TX, USA) at 25°C for 2 h. The loaded cells were then washed four times with, and finally incubated in, Tyrode's medium (NaCl, 145 mM; KCl, 2.5 mM; HEPES, 10 mM; glucose, 10 mM; $MgCl_2$, 1.2 mM; $CaCl_2$, 1.5 mM) containing 0.2% BSA, before being incubated for 30 min at 25°C with either buffer alone or buffer containing various antagonists. The plates were then placed into a FLIPR™ (Molecular Devices, UK) to monitor cell fluorescence (λ_{ex}=488 nm, λ_{EM}=540 nm)[14] before and after the addition of various vanilloid or cannabinoid agonists.

Dissociated rat neonatal DRG cells were seeded into black walled clear-base 384-well plates (Costar, UK) at a density of 10 000 cells per well and incubated with Tyrodes buffer containing Fluo-4 at 37°C for 1 h. DRG cells were then washed as described previously before incubation with buffer alone of buffer containing antagonists at 25°C for 30 min. Cells were then placed into the FLIPR™ and fluorescence monitored as described above before and after the addition of various vanilloid or cannabinoid agonists. It is noteworthy that the use of Fluo-4 is required in DRG cells in 384-well plate format, compared with Fluo-3 for rVR1-HEK293 cells, to obtain a signal of sufficient magnitude.

Measurement of cyclic AMP production

DRG cells were incubated with cannabinoid agonists (100 nM) for 15 min at 37°C. The cells were then exposed to Forskolin (3 μM) for 20 min and the levels of cAMP determined, using a cAMP enzyme immunoassay kit system (Amersham, cat. no. RPN 225).

Data analysis

Functional responses using FLIPR were measured as peak fluorescence intensity minus basal fluorescence and, where appropriate, expressed as a percentage of a maximum capsaicin-induced response on the same plate. Iterative curve-fitting and parameter estimations were carried out using a four parameter logistic model and Microsoft Excel.[15] Antagonist potency values (IC_{50}) were converted

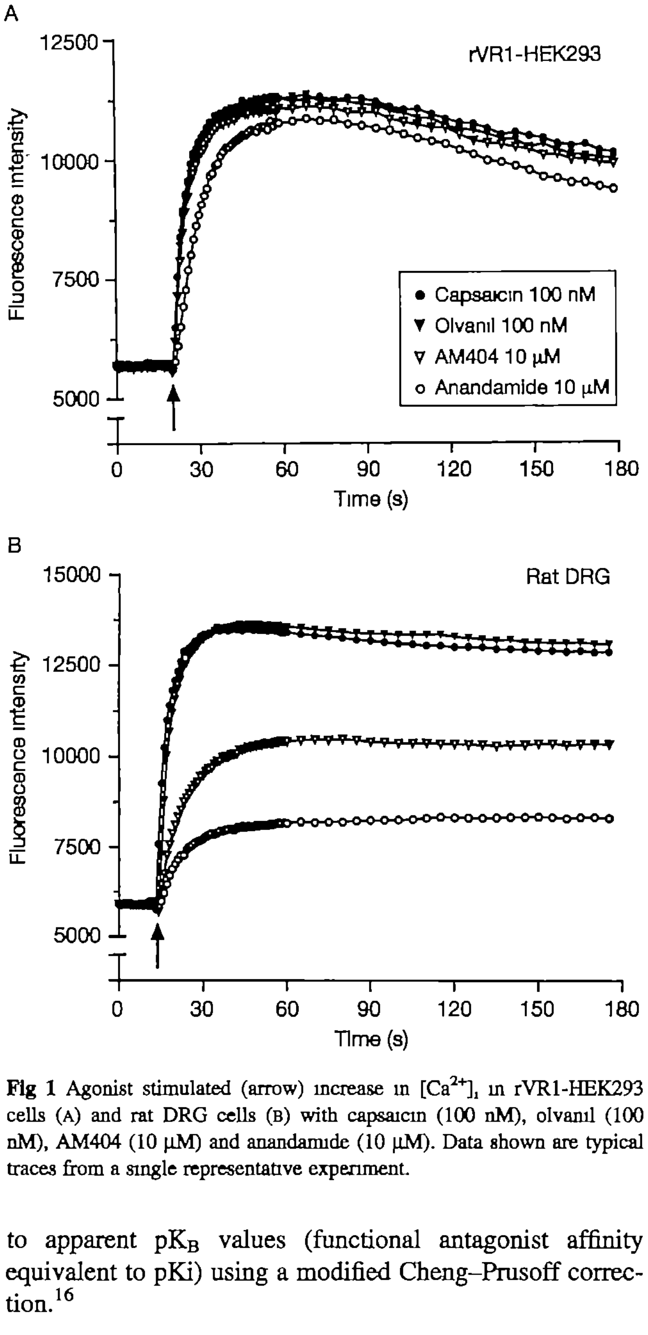


Fig 1 Agonist stimulated (arrow) increase in $[Ca^{2+}]_i$ in rVR1-HEK293 cells (A) and rat DRG cells (B) with capsaicin (100 nM), olvanil (100 nM), AM404 (10 μM) and anandamide (10 μM). Data shown are typical traces from a single representative experiment.

to apparent pK_B values (functional antagonist affinity equivalent to pKi) using a modified Cheng–Prusoff correction.[16]

$$\text{Apparent } pK_B = -\log \frac{(IC_{50})}{1+\frac{[agonist]}{(EC_{50})}}$$

Data are expressed as mean (SEM) unless otherwise stated. Statistical tests for significance were conducted using two-way analysis of variance.

Materials

Anandamide (arachidonoyl-ethanolamide), AM404 (*N*-(4-hydroxyphenyl-arachinoylamide) and all other cannabinoids (AM630, AM251, AM281, HU210, WIN55, ZIZ-Z, CP55, G40) were obtained from Tocris (Bristol, UK). Capsaicin, capsazepine, olvanil (*N*-vanillyl-*cis*-9-octadecenoamide) and all bulk reagents were obtained from Sigma-Aldridge Ltd (Poole, Dorset, UK). All cell culture media were obtained from Life Technologies (Paisley, UK).

Results

Capsaicin, olvanil, anandamide and AM404 increased $[Ca^{2+}]_i$ when applied to rVR1-HEK and to rat DRG cells (Fig. 1). The temporal profiles of responses to capsaicin and olvanil in both cell types were comparable and were typified by an initially rapid then slowing onset (peak ~30 s) followed by a slowly declining phase (Fig. 1). The temporal profile of responses to anandamide and AM404 were also similar in both cell types although responses in DRG cells were more sustained than that in the recombinant system. Responses to all agonists were concentration dependent, with a rank order of potency of capsaicin = olvanil > AM404 > anadamide in both cell types, although potencies determined in rVR1-HEK cells tended to be higher (~0.8 log units) than those in DRG cells (Fig. 2 and Table 1). In the rVR1-HEK cells all agents were full agonists compared with capsaicin whereas AM404 was a partial agonist, compared with capsaicin, when tested in rat DRG cells (Fig. 2). Similarly, anandamide was less efficacious in DRG cells compared with rVR1-HEK cells, although the absolute efficacy of anandamide in DRG cells is difficult to determine as concentration–response curves were bell shaped. The absence of a defined saturable response for anandamide in DRG cells, complicates determination of a meaningful potency value (Table 1).

The competitive VR1 antagonist capsazepine and the poreblocker ruthenium red inhibited capsaicin-induced responses in a concentration-dependent manner with pK_B values of 7.21 (0.06) and 8.54 (0.08) in rVR1-HEK cells and 6.42 (0.02) and 8.60 (0.06) in rat DRG cells, respectively. In rVR1-HEK cells the antagonist affinity of capsazepine was not significantly different when inhibiting capsaicin-, olvanil-, AM404- or anandamide-induced responses with pK_B values of 7.21 (0.06), 7.35 (0.06), 7.18 (0.03) and 7.40 (0.12), respectively.

Incubation with capsazepine (10 μM) or ruthenium red (1 μM) significantly inhibited ($P<0.01$) subsequent responses to capsaicin (300 nM) and anandamide (10 μM) in rat DRG cells (Table 2). In contrast to this, pre-incubation with the cannabinoid antagonists AM630, AM251, AM281,[17] or cannabinoid agonists HU210, WIN 55,212-2 or CP 55,940[3,18] (10 μM) did not significantly alter the magnitude of subsequent capsaicin- or anandamide-induced responses (Table 2).

Application of the synthetic cannabinoid agonists HU210, WIN 55,212-2 or CP 55,940 (1 μM) failed to induce an increase in $[Ca^{2+}]_i$ in either cell type (data not shown), whereas pre-application of either capsaicin (1 μM)

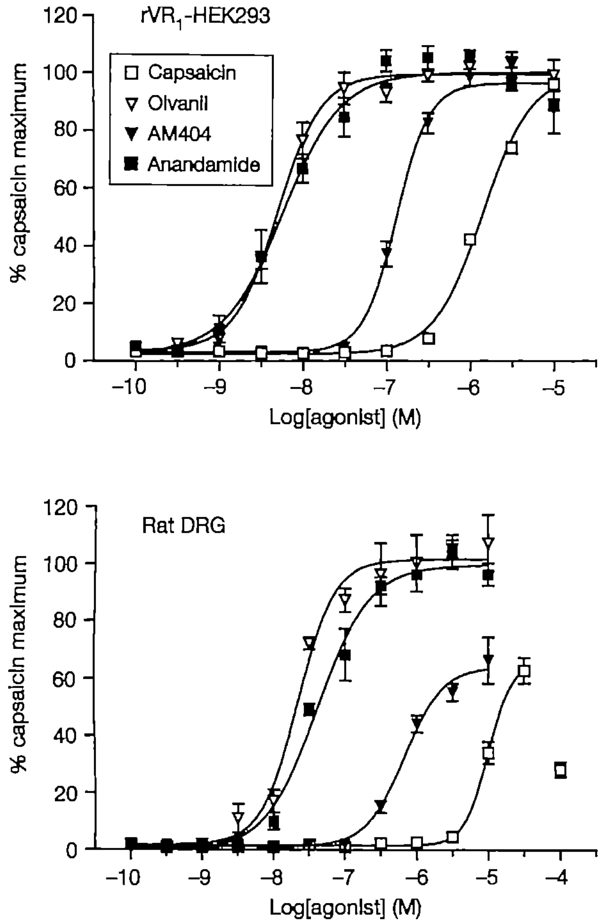


Fig 2 Agonist stimulation (arrow), relative to capsaicin maximal response, in rVR1-HEK293 cells (A) and RDG cells (B) with capsaicin, olvanil, AM404 and anandamide. Data are mean (SEM) from at least three independent experiments

or anandamide (10 μM) significantly reduced (P<0.01) the magnitude of subsequent capsaicin (300 nM) and anandamide (10 μM) responses in DRG cells (Table 2).

In DRG cells, application of the cannabinoid agonist HU210 or CP 55,940 (1 μM) did not significantly (P<0.01) inhibit forskolin-induced cAMP production, with cAMP levels of 359 (103), 373 (101) and 376 (43) fmol, respectively (n=3).

Discussion

VR1 receptors have been identified as a receptor for the endogenous cannabinoid anandamide in studies using both recombinant receptors[10 19] and isolated tissue preparations.[11] In the present study, using a common methodology we have compared the *in vitro* pharmacology of recombinant rat VR1 receptors with that of endogenous VR1 in primary DRG cells. We have also considered the relative contribution of CB_1 and VR1 receptors to anadamide-induced responses.

Table 1 Agonist potencies (pEC_{50}) or per cent stimulation (30 μM, relative to capsaicin) of increases in $[Ca^{2+}]_i$ in rVR1 expressing HEK293 cells and in dissociated rat neonatal DRG cultures. Data are mean (SEM) from four to eight independent experiments

	rVR1-HEK293	**Rat DRG**
Capsaicin	8.25 (0.11)	7.45 (0.10)
Anandamide	5.85 (0.01)	63%
AM404	6.96 (0.06)	6.10 (0.13)
Olvanil	8.37 (0.04)	7.55 (0.07)

Table 2 Effects of 30 min pre-incubation with vanilloid and cannabinoid ligands on subsequent capsaicin- or anandamide-induced $[Ca^{2+}]_i$ responses in DRG cells. Data are mean (SEM), n=4; *P<0.01 *vs* control

	Per cent stimulation	
	***vs* Capsaicin (300 nM)**	***vs* Anandamide (10 μM)**
Control	100 (3)	100 (5)
Capsazepine (10 μM)	3 (5)*	9 (1)*
Ruthenium red (1 μM)	28 (3)*	38 (8)*
Capsaicin (1 μM)	12 (2)*	23 (2)*
Anandamide (10 μM)	24 (4)*	16 (4)*
AM630 (1 μM)	102 (10)	120 (9)
AM251 (1 μM)	99 (5)	102 (19)
AM281 (1 μM)	115 (5)	100 (12)
WIN 55,212-2 (1 μM)	108 (8)	107 (10)
CP 55,940 (1 μM)	105 (7)	101 (11)
HU210 (1 μM)	91 (11)	116 (16)

In the present study capsaicin, olvanil, anandamide and AM404 induced a concentration-dependent increase in $[Ca^{2+}]_i$ and the kinetics of responses in rVR1-HEK cells were virtually identical compared with those in rat DRG cells (Fig. 1). Similarly, agonist rank order of potency was also maintained between the two cell types and was consistent with that of previous reports.[12] The observation that agonist potencies were higher in rVR1-HEK cells (~0.8 log units) and the fact that anandamide and AM404 were less efficacious in DRG cells compared with rVR1-HEK cells, is readily explained by accepted receptor theory and suggests the presence of receptor reserve in the latter. However, the relatively low efficacy of anandamide in the DRG cells, and the fact that concentration–response curves to anandamide were bell-shaped in these cells, complicates determination of maximal efficacy. Moreover, in the present study it is impossible to determine if anandamide is a partial agonist in the DRG cells. However, it is likely that the bell-shaped concentration–response curves to anandamide reflect the relative insolubility of this compound at higher concentrations. In the present study responses to 30 μM anandamide, which represents the highest achievable concentration without encountering solubility problems, were approximately 60% relative to that of capsaicin (1 μM). The data are in agreement with data from electrophysiological studies using VR1 expressing HEK293 cells and *Xenopus* oocytes.[11] The physiological significance of the relative efficacy of anandamide in this study, and the relevance to the efficacy in man, has yet to be determined. It is noteworthy that the apparent affinity of capsazepine, but not ruthenium red, was lower in the DRG preparation than that in rVR1-HEK293 cells. The reason(s) for this remain unclear, but may reflect secondary modulation of the binding sites associated with the differing cellular environment.

Taken collectively the data are consistent with VR1-mediation of responses seen in both recombinant and DRG cells. However, several aspects of the present study provide evidence against the involvement of cannabinoid receptors in responses in the DRG cells. No inhibition of forskolin-induced cAMP production, nor any increase in [Ca^{2+}]$_i$, was seen following the application of potent CB$_1$ receptor agonists,[3,18] despite immunocytochemical evidence of CB$_1$ expression in DRG neurones.[20] Furthermore, neither the cannabinoid antagonists AM630, AM251 and AM281,[17] nor the CB$_1$ receptor agonists HU210, WIN 55,212-2 and CP 55,940[3,18] had any effect on either capsaicin- or anandamide-induced responses in DRG cells. In addition, the potency of anandamide in the present study (>10 μM) is considerably lower than the binding affinity (55 nM) reported for anandamide at CB$_1$ receptors.[4] In contrast, pre-application of known VR1 antagonists such as capsazepine[9] and ruthenium red[21] significantly inhibited a subsequent response to capsaicin and anandamide.

In the present study we have provided evidence that vanilloid pharmacology is similar in recombinant and physiologically relevant systems *in vitro*. We have also provided evidence that anandamide induces response in DRG cells that are VR1, but not CB$_1$ receptor-mediated. It is reasonable, therefore, to conclude that anandamide may interact with vanilloid receptors *in vivo* leading to receptor desensitization and analgesia, as proposed previously,[22,23] but this remains controversial.[24] Overcoming the technical difficulties in handling poorly soluble lipid compounds such as anandamide, will contribute greatly to the resolution of this controversy.

Nevertheless, it is clear that regarding the cannabinoid and vanilloid receptor systems as two completely separate entities, at least in their respective contribution to analgesia, is unwise. It could be argued that these two receptors share a common pharmacophore and that this is purely coincidental. On the other hand, though purely speculative, it is also tempting to consider that these receptors represent different classes of the same receptor system, somewhat analogous to the ionotropic and metabotropic classes of glutamate receptors.

Evidence that a physiological link exists between VR1 and CB$_1$ receptors is lacking in our data. In the present study, selective CB$_1$ agonists and antagonists had no feedback effects on subsequent VR1 activity. However, considering the possibility that the cannabiniod and the vanilloid systems are interlinked in the same physiological responses and share common pharmacophores, affords the possibility of development of novel analgesics with high therapeutic potential. A non-pungent VR1 receptor agonist that is also a CB$_1$ receptor agonist for example, may be efficacious in the treatment of pain.

Alternative approaches are also being considered.[25] For example, modulation of anandamide biosynthesis and inactivation, such as inhibition of anandamide hydrolysis, may also provide useful therapeutics.[25] However, as is the case with all cannabinoid targeted drug therapies the contribution of the vanilloid system must not be overlooked.

References

1. Devane WA, Dysarz FA, Johnson MR, *et al.* Determination and characterization of a cannabinoid receptor in rat brain. *Mol Pharmacol* 1988; **34**: 605–13
2. Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. *Nature* 1993; **365**: 61–5
3. Pertwee RG. Pharmacology of cannabinoid CB$_1$ and CB$_2$ receptors. *Pharmacol Ther* 1997; **74**: 129–80
4. Devane WA, Hanus L, Breuer A, *et al.* Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science* 1992; **258**: 1946–9
5. Mechoulam R, Ben-Shabat S, Hanus L, *et al.* Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. *Biochem Pharmacol* 1995; **50**: 83–90
6. Sugiura T, Kondo S, Sukagawa A, *et al* 2-Arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain. *Biochem Biophys Res Commun* 1995; **215**: 89–97
7. Adams IB, Compton DR, Martin BR. Assessment of anandamide interaction with the cannabinoid brain receptor: SR 141716A antagonism studies in mice and autoradiographic analysis of receptor binding in rat brain. *J Pharmacol Exp Ther* 1998; **284**: 1209–17
8. Di Marzo V, Breivogel CS, Tao Q, *et al.* Levels, metabolism, and pharmacological activity of anandamide in CB$_1$ cannabinoid receptor knockout mice: evidence for non-CB$_1$, non-CB$_2$ receptor-mediated actions of anandamide in mouse brain. *J Neurochem* 2000; **75**: 2434–44
9. Szallasi A, Blumberg PM. Vanilloid (Capsaicin) receptors and mechanisms. *Pharmacol Rev* 1999; **51**: 159–212
10. Smart D, Gunthorpe MJ, Jerman JC, *et al* The endogenous lipid anandamide is a full agonist at the human vanilloid receptor (hVR1). *Br J Pharmacolol* 2000; **129**: 227–30
11. Zygmunt PM, Petersson J, Andersson DA, *et al.* Vanilloid receptors on sensory nerves mediate the vasodilator action of anandamide. *Nature* 1999, **400**: 452–7
12. Jerman JC, Brough SJ, Prinjha R, *et al.* Characterization using FLIPR of rat vanilloid receptor (rVR1) pharmacology. *Br J Pharmacolol* 2000; **130**: 916–22
13. Skaper SD, Facci L, Milani D. Culture and use of primary and clonal neuronal cells. In: Conn PM, ed. *Methods in Neurosciences*, Vol. 2. San Diego: Academic Press, 1990; 17–33
14. SullivanE, Tucker EM, Dale IL. Measurement of [Ca^{2+}]$_i$ using the fluometric imaging plate reader (FLIPR). In: Lambert DG, ed. *Calcium Signaling Protocols*. New Jersey: Humana Press, 1999; 125–136
15. Bowen WP, Jerman JC. Nonlinear regression using spreadsheets. *Trends Pharmacol Sci* 1995; **16**: 413–7
16. Cheng YC, Prusoff WH. Relationship between the inhibition constant (K$_i$) and the concentration of inhibitor which causes 50

per cent inhibition (IC_{50}) of an enzymatic reaction. *Biochem Pharmacol* 1973; **22**: 3099–108

17 Lan R, Liu Q, Fan P, *et al.* Structure-activity relationships of pyrazole derivatives as cannabinoid receptor antagonists. *J Med Chem* 1999; **42**: 769–76

18 Huffman JW, Lainton JAH. Recent developments in the medicinal chemistry of cannabinoids *Curr Med Chem* 1996; **3**. 101–16

19 Jerman JC, Brough SJ, Davis JB, *et al.* The endogenous lipid anandamide is an agonist at rat and human vanilloid (VR1) receptors. *Eur J Neurosci* 2000; **12** (Suppl. 11): 59.10

20 Ahluwalia J, Urban L, Capogna M, *et al.* Cannabinoid 1 receptors are expressed in nociceptive primary sensory neurons. *Neuroscience* 2000; **100**: 685–8

21 Jung YS, Cho TS, Moon CH, *et al.* Capsaicin-induced desensitization is prevented by capsazepine but not by ruthenium red in guinea pig bronchi. *Eur J Pharmacol* 1998; **362**: 193–8

22 Zygmunt PM, Julius I, Di Marzo I, *et al.* Anandamide—the other side of the coin. *Trends Pharmacol Sci* 2000; **21**: 43–4

23 Smart D, Jerman JC. Anandamide: an endogenous activator of the vanilloid receptor. *Trends Pharmacol Sci* 2000; **21**: 134

24 Szolcsanyi J. Anandamide and the question of its functional role for activation of capsaicin receptors. *Trends Pharmacol Sci* 2000; **21**: 203–4

25 Di Marzo V, Bisogno T, De Petrocellis L. Endocannabinoids· new targets for drug development. *Curr Pharmaceutical Des* 2000; **6**: 1361–80

British Journal of Anaesthesia **89** (6): 888–95 (2002)

Electrophysiological effects of morphine in an *in vitro* model of the 'border zone' between normal and ischaemic–reperfused guinea-pig myocardium

A. Yvon[1], J.-L. Hanouz[2]*, X. Terrien[1], P. Ducouret[1], R. Rouet[1], H. Bricard[2] and J.-L. Gérard[1]

[1]Laboratory of Experimental Anesthesiology and Cellular Physiology, UPRES EA 3212, Centre Hospitalier Universitaire, Côte de Nacre, Caen, France. [2]Department of Anesthesiology, Centre Hospitalier Universitaire, Caen, France

**Corresponding author: Département d'Anesthésie-Réanimation, CHU de Caen, Avenue Côte de Nacre, F-14033 Caen Cedex, France. E-mail: hanouz-jl@chu-caen.fr*

Background. Morphine is commonly used in clinical practice in pain management. Although morphine has been shown to precondition the myocardium, its effects on action potential parameters and ischaemia–reperfusion-induced arrhythmias and conduction blocks remain unknown.

Methods. In a double-chamber bath, guinea-pig right ventricular muscle strips were subjected partly to normal conditions and partly to 30 min of simulated ischaemia (hypoxia, hyperkalaemia, acidosis, and lack of nutritional substrate) followed by 30 min of reperfusion. Action potential parameters were recorded continuously in the normal zone and in the ischaemic–reperfused zone. Spontaneous arrhythmias and conduction blocks were noted. The electrophysiological effects of morphine were studied at 0.01 and 0.1 µM.

Results. In control conditions, morphine did not modify action potential parameters of resting membrane potential, maximal upstroke velocity (V_{max}), action potential amplitude (APA) and action potential duration at 50 and 90% of repolarization. Morphine reduced ischaemia-induced depolarization and lessened the ischaemia-induced decrease in APA and V_{max}. Morphine significantly decreased the occurrence of conduction block during simulated ischaemia (20% at 0.01 and 0.1 µM *vs* 67% in the control group, $P<0.05$) and reperfusion-induced arrhythmias (40% at 0.01 µM and 30% at 0.1 µM *vs* 92% in the control group, $P<0.05$).

Conclusions. In ischaemic–reperfused guinea-pig myocardium, morphine at clinically relevant concentrations decreased ischaemia-induced conduction blocks and reperfusion-induced ventricular arrhythmias.

Br J Anaesth 2002; **89**: 888–95

Keywords: analgesics opioid, morphine; heart, arrhythmia; heart, ischaemia; heart, reperfusion injury

Accepted for publication: July 23, 2002

Morphine, a µ-opioid receptor agonist, is used in daily clinical practice in the management of pain during acute myocardial infarction and in the postoperative period, when it is known to be associated with a high risk of myocardial ischaemia in patients with known or unknown coronary artery disease.[1] A growing body of evidence suggests that opioid receptor stimulation may have cardioprotective effects.[2–4] However, the clinical relevance of studies dealing with opioid-induced preconditioning remains limited, because in acute myocardial infarction morphine is administered during or after, but rarely before, myocardial ischaemia. Similarly, in the postoperative period myocardial ischaemia may occur even though patients are treated with morphine. Moreover, because ischaemia-induced ventricular arrhythmias are potentially fatal complications of myocardial ischaemia, it is important to examine the effects of morphine on ischaemia- and reperfusion-induced arrhythmias. The main mechanisms involved in ventricular

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

arrhythmias related to myocardial ischaemia are abnormal automaticity and re-entrant rhythms.[5] Rouet and colleagues developed an *in vitro* model simulating the 'border zone' between normal and ischaemic–reperfused ventricular myocardium,[6] providing the opportunity to study ischaemia-related conduction blocks and reperfusion-induced spontaneous arrhythmias.[7]

The purpose of our study was to examine the effect of clinically relevant concentrations of morphine administered during ischaemia and reperfusion on the time-course parameters of the action potential and on the incidence of arrhythmias in isolated guinea-pig myocardium.

Material and methods

Animal care was in agreement with the recommendations of the Helsinki Declaration and the study was performed in accordance with the official edict of the French Ministry of Agriculture.

Guinea-pigs of either sex weighing 300–400 g were killed by cervical dislocation after brief ether anaesthesia, and immediately exsanguinated. The heart was quickly removed at room temperature into oxygenated Tyrode's solution containing (mM) 135 Na^+, 4 K^+, 1.8 Ca^{2+}, 1.8 $H_2PO_4^-$, 25 HCO_3^-, 117.8 Cl^- and 5.5 glucose.

A myocardial strip (15 mm long, 5 mm wide, 1.5 mm thick) was carefully dissected from the free wall of the right ventricle. The strip was pinned, endocardial surface upwards, in a special perfusion chamber. This chamber (5 ml) was bisected by a thin latex membrane including a centrally located hole that allowed the preparation to be passed through and divided into two zones, called the normal zone (NZ) and the altered zone (AZ). The two compartments were perfused independently by a peristaltic pump at 2 ml min^{-1}, bubbled with carbogen (95% oxygen, 5% carbon dioxide). The pH of the Tyrode's solution was equilibrated to 7.35 (0.05) with dilute hydrochloric acid and the temperature was maintained at 36.5°C with a water-circulating thermostat-controlled bath (Polystat 5HP; Bioblock, Illkirch, France). To check for the absence of leakage between the two compartments, we injected methylene blue dye into one compartment after the experiment.

Data acquisition and analysis

Preparations were stimulated at 1 Hz with two bipolar silicon-coated electrodes positioned in the NZ and in the AZ. A commutator allowed stimulation of the preparation through one or the other stimulating electrode. Stimuli were rectangular pulses of 1–2 V depolarizing voltage, duration 2 ms, delivered by a programmable stimulator (model SMP 310; Biologic, Grenoble, France). Preparations that needed pulses stronger than 5 V to elicit action potentials were discarded because there could have been a conduction block at the level of the latex separating membrane. During the protocol, stimulation was stopped whenever sustained spontaneous arrhythmias occurred. Action potential parameters were recorded simultaneously in both myocardial regions using glass microelectrodes pulled from borosilicate filament tubes (GC 200F-15; Phymep, France) on a single-barrelled microelectrode puller (Narashige, distributed by OSI, France). Microelectrodes were filled with potassium chloride 3 M (tip resistance 10–30 MΩ) and coupled to a silver–silver chloride microelectrode holder leading to a home-built, high-impedance capacitance-neutralizing amplifier. A ball-shaped reference silver–silver chloride electrode was positioned in the superfusate of each compartment.

Action potentials (AP) were monitored on a digital oscilloscope (Gould Instrument Systems, Cleveland, OH, USA). The following AP parameters were automatically stored and measured using a cardiac AP automatic acquisition system and processing device (Datapac; Biologic): resting membrane potential (RMP); action potential amplitude (APA), action potential duration at 50% of full repolarization (APD_{50}); action potential duration at 90% of full repolarization (APD_{90}); and maximal upstroke velocity (V_{max}). Whenever possible, the same impalement was maintained throughout the experiment; when it was lost, readjustment was attempted. If the readjusted parameters differed by less than 10% from previous values, experiments were continued; otherwise they were terminated.

Experimental protocol

After a 2 h equilibration period (when AP parameters were stabilized), simulated ischaemia was induced for 30 min in the AZ compartment by superfusion with modified Tyrode's solution, while the NZ compartment was maintained in normal conditions. The modified Tyrode's solution differed from normal by elevated potassium concentration (from 4 to 12 mM), decreased HCO_3^- concentration (from 25 to 9 mM), leading to a decrease in pH [from 7.35 (0.05) to 6.90 (0.05)], and decreased PO_2 by replacement of 95% oxygen–5% carbon dioxide with a gas mixture containing 95% nitrogen and 5% carbon dioxide and withdrawal of glucose. These modifications, combining hypoxia, hyperkalaemia, acidosis and lack of substrate, reproduced *in vitro* the electrophysiological abnormalities induced *in vivo* by ischaemia [6 8–14] After 30 min of simulated ischaemia, a 30 min reperfusion period was initiated by reperfusing Tyrode's solution rebubbled with 95% oxygen–5% carbon dioxide mixture.

During both simulated ischaemia and reperfusion, conduction disturbances[10 13] and arrhythmias[6 10 13] were recorded: (i) conduction blocks between the AZ and the NZ; (ii) spontaneous arrhythmias independent of stimulation [one or two extrasystoles, salvos (3–10 AP), sustained activities (>10 AP)]; and (iii) loss of responsiveness to a constant stimulation intensity. Stimulation was stopped whenever sustained arrhythmias occurred.

Table 1 Effects of morphine on the action potential parameters in the 'normal zone'. Data are mean (SD). RMP=resting membrane potential; V_{max}=maximal upstroke velocity of action potential, APA=action potential amplitude; APD_{50} and APD_{90}=action potential duration at 50 and 90% of repolarization respectively

	Control (n=12)	Morphine 0.01 µM (n=10)	Morphine 0.1 µM (n=10)
RMP (mV)			
Initial	–94 (4)	–97 (3)	–93 (3)
30 min	–94 (4)	–95 (5)	–94 (3)
60 min	–94 (4)	–97 (5)	–96 (4)
V_{max} (mV s^{-1})			
Initial	257 (87)	306 (94)	306 (133)
30 min	188 (37)	271 (62)	264 (124)
60 min	212 (59)	278 (51)	282 (103)
APA (mV)			
Initial	119 (5)	123 (4)	120 (6)
30 min	119 (4)	120 (8)	121 (5)
60 min	120 (6)	124 (4)	121 (6)
APD_{50} (ms)			
Initial	114 (21)	104 (28)	107 (10)
30 min	113 (26)	98 (29)	98 (15)
60 min	122 (23)	96 (26)	111 (15
APD_{90} (ms)			
Initial	141 (21)	131 (35)	138 (11)
30 min	140 (25)	125 (36)	132 (12)
60 min	151 (22)	138 (34)	145 (12)

During the simulated ischaemia and reperfusion phases, Tyrode's solution with 0.01 or 0.1 µM morphine (n=10 for each group) added or Tyrode's solution alone (n=12) was superfused randomly in both compartments (NZ and AZ). Thus, the electrophysiological effects of morphine on AP parameters and the incidence of arrhythmias were investigated simultaneously in normal (NZ) and altered (AZ) conditions.

Statistical analysis

All results are expressed as mean (SD). Multiple comparison of continuous variables was performed by repeated-measures analysis of variance followed by comparison with control or initial values (measurement before initiation of the ischaemic period) using the Bonferroni *post hoc* test. Fisher's exact test was used for comparison of non-parametric categorical data. All P values were two-tailed, and P<0.05 was required to reject the null hypothesis.

Results

Ischaemia and reperfusion effects on action potential parameters

In the NZ, all AP parameters recorded remained unchanged during 60 min of superfusion with normal Tyrode's solution (Table 1). Simulated ischaemia-induced alterations of AP parameters are summarized in Table 2. In the control group, 5 min of simulated ischaemia induced significant membrane depolarization [–27 (5)% of baseline, P<0.01], significant decreases in V_{max} [–62 (14)% of baseline, P<0.01] and APA [–28 (10)% of baseline, P<0.01], and significant decreases in APD_{50} [–70 (10)% of baseline, P<0.01] and APD_{90} [–66 (10)% of baseline, P<0.01]. The maximal electrophysiological modifications reached a plateau within the first 10 min. Reperfusion of the AZ was associated with rapid recovery of the AP parameter values (Table 2).

Morphine effects on action potential parameters in normoxic conditions

As shown in Table 1, there were no differences in initial values of AP parameters between experimental groups. In the NZ, morphine at 0.01 and 0.1 µM did not modify the AP parameters RMP, V_{max}, APA, APD_{50} and APD_{90} (Table 1).

Morphine effects on action potential parameters in ischaemic–reperfused simulated conditions

Morphine reduced the ischaemia-induced depolarization [–29 (5)% and –24 (5)% in the presence of morphine 0.01 and 0.1 µM respectively, compared with –32 (1)% for the control group after 30 min of ischaemia; P<0.001 for each group]. The ischaemia-induced decrease in APA [–31 (5)% and –27 (6)% in the presence of morphine 0.01 and 0.1 µM respectively, compared with –39 (9)% for the control group after 30 min of ischaemia; P<0.001 for each group] and V_{max} [–54 (7)% and –56 (12)% in the presence of morphine 0.01 and 0.1 µM respectively, compared with –71 (19)% in the control group after 30 min of ischaemia; P<0.001 for each group] were significantly attenuated by morphine. As shown in Table 2, the ischaemia-induced AP shortenings were not affected by morphine whatever the concentration tested. At the end of the reperfusion, RMP, APA, V_{max},

Table 2 Effects of morphine on the action potential parameters during simulated ischaemia and reperfusion in the abnormal zone Data are mean (SD) $^{*}P<0.01$ baseline value *vs* value at the end of ischaemia and reperfusion; $^{\dagger}P<0.05$ and $^{\ddagger}P<0.01$ morphine groups *vs* control group. RMP=resting membrane potential; V_{max}=maximal upstroke velocity, APA=action potential amplitude, APD_{50} and APD_{90}=action potential duration at 50 and 90% of repolarization respectively

	Control (*n*=12)	**Morphine 0.01 μM** (*n*=10)	**Morphine 0.1 μM** (*n*=10)
RMP (mV)			
Initial	−91 (4)	−97 (4)	−95 (3)
Ischaemia 30 min	−62 (3)*	−68 (3)*‡	−72 (3)*‡
Reperfusion 30 min	−92 (2)	−100 (6)	−97 (5)
V_{max} (mV s^{-1})			
Initial	214 (50)	267 (75)	327 (95)
Ischaemia 30 min	56 (32)*	121 (54)*‡	147 (27)*‡
Reperfusion 30 min	187 (49)	249 (52)	295 (89)
APA (mV)			
Initial	122 (6)	124 (6)	123 (4)
Ischaemia 30 min	75 (11)*	86 (6)*‡	89 (6)*‡
Reperfusion 30 min	120 (5)	126 (3)	122 (3)
APD_{50} (ms)			
Initial	113 (24)	96 (19)	113 (9)
Ischaemia 30 min	36 (20)*	30 (11)*	46 (14)*
Reperfusion 30 min	118 (16)	89 (13)	118 (7)
APD_{90} (ms)			
Initial	138 (22)	123 (20)	141 (8)
Ischaemia 30 min	53 (17)*	47 (14)*	62 (13)*†
Reperfusion 30 min	148 (14)	118 (16)	148 (8)

APD_{50} and APD_{90} in the AZ reached baseline values and were comparable between groups (Table 2).

Morphine effects on ischaemia–reperfusion-induced conduction disturbances

As shown in Figure 1, conduction blocks occurred after 15 (7) min in the control group, 16 (14) min in the presence of 0.01 μM morphine and after 21 (7) min in the presence of 0.1 μM morphine. At the end of the ischaemic period there was no significant difference between groups in the incidence of loss of responsiveness (1% for control group and 0% for the morphine groups). Reperfusion of AZ induced complete recovery of responsiveness in all experimental groups.

As summarized in Figure 2, morphine 0.01 and 0.1 μM significantly decreased the occurrence of conduction block during the 30 min ischaemic period (20% for morphine groups *vs* 67% for the control group, $P<0.01$). In each group, conduction blocks disappeared during the reperfusion period.

Morphine effects on ischaemia–reperfusion-induced arrhythmias

As illustrated in Figures 1 and 2, during the ischaemic period the number of preparations exhibiting spontaneous repetitive responses was not modified in the presence of morphine. During the reperfusion period, the occurrence of spontaneous repetitive responses was significantly decreased in the presence of morphine 0.01 and 0.1 μM (40% in the presence of 0.01 μM morphine and 30% in the presence of morphine 0.1 μM *vs* 92% in the control group; $P<0.05$).

Discussion

This study showed that: (i) morphine reduced ischaemia-induced membrane depolarization and attenuated the ischaemia-induced decrease in APA and V_{max}; (ii) morphine decreased the occurrence of conduction block during simulated ischaemia; and (iii) morphine decreased the occurrence of reperfusion-induced arrhythmias.

Our results show that morphine did not affect AP parameters in normoxic conditions. This is in accordance with previous results showing that morphine, even at high concentrations, did not significantly modify electrophysiological parameters recorded on isolated myocardium.[15 16] Although Hung and colleagues have shown that morphine decreases the sodium inward current (I_{Na}) in human and rat isolated myocytes, this effect became significant at concentrations 100-fold higher than those tested in our study.[17] Additionally, Hung and colleagues showed that morphine at 30 μM did not affect the inward calcium current, the transient outward potassium current or the inwardly rectifying potassium currents.[17] In our study we tested the effects of morphine 0.01 and 0.1 μM because these concentrations are in the range of plasma concentrations measured in clinical practice, taking the protein binding of morphine into account.[18] To our knowledge, there are no studies dealing with the effects of clinically relevant concentrations of

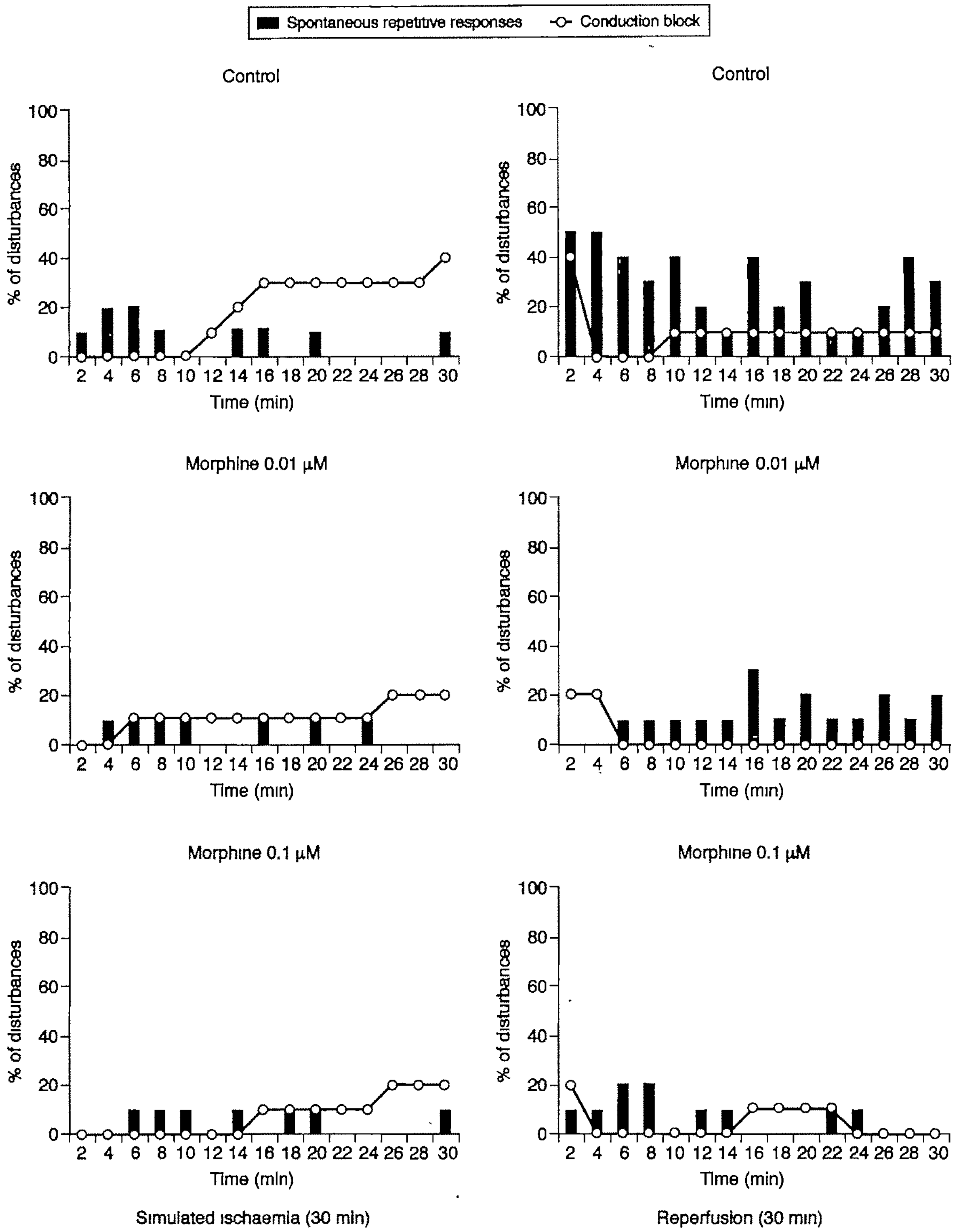


Fig 1 Effects of morphine on the incidence of conduction block and arrhythmia during simulated ischaemia (left panels) and reperfusion (right panels) Every 2 min during the ischaemic period (30 min) and the reperfusion period (30 min), values are expressed as percentages of preparations presenting conduction blocks between the two myocardial regions and spontaneous arrhythmias, defined as disturbances. Results are reported in the absence of drug (top panels) and in the presence of 0.01 μM (middle panels) and 0.1 μM morphine (bottom panels).

morphine on ion transmembrane currents in myocardial cells.

Our results confirm the ischaemia-induced decrease in RMP and AP parameters reported previously in similar studies.[6 7 10] Furthermore, in AZ the ischaemia-induced decrease in RMP was attenuated by morphine at 0.01 and 0.1 μM. It is well known that depolarization of the RMP can lead to steady-state inactivation and slower

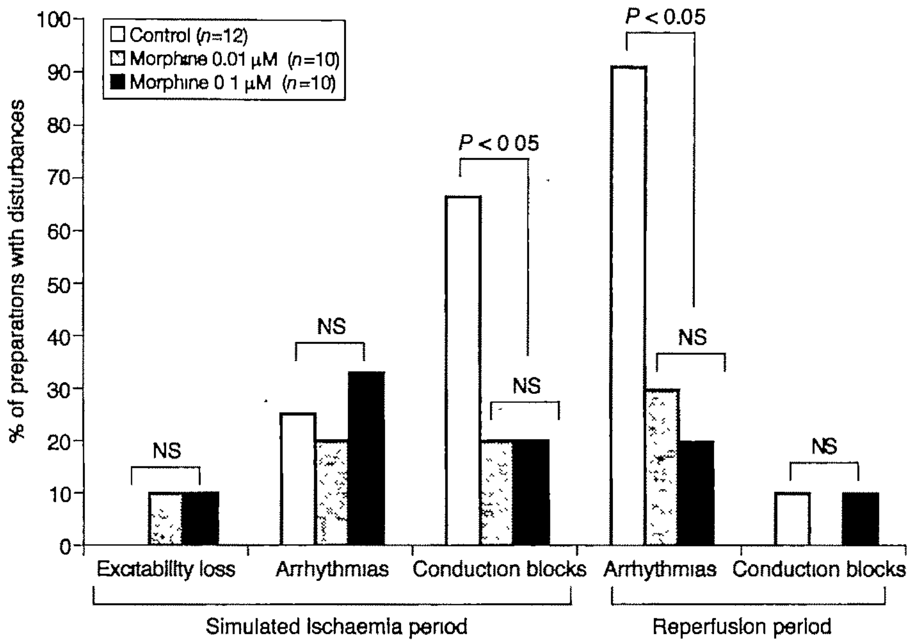


Fig 2 Effects of morphine on the incidence of loss of responsiveness to constant stimulation intensity, arrhythmias and conduction blocks during simulated ischaemia and reperfusion periods. Data are expressed as percentage of preparations with disturbances during the experiments.

reactivation of sodium channels, thereby reducing the number of channels available to carry I_{Na} during the action potential upstroke. Consequently, attenuated ischaemia-induced membrane depolarization measured in the presence of morphine should attenuate the ischaemia-induced decrease in I_{Na}, and thus the decreases in V_{max} and APA. This is in agreement with our results showing that morphine attenuated the decrease in V_{max} and APA measured during simulated ischaemia. Because depolarizing the RMP plays a pivotal role in the production of re-entrant arrhythmias during the acute phase of ischaemia,[14] this result could explain, at least in part, the anti-arrhythmic effect of morphine reported here and in previous studies.[2 19 20] Our study shows that morphine did not modify the ischaemia-induced decrease in APD_{50} and APD_{90}. Although morphine 0.1 μM significantly attenuated the ischaemia-induced decrease in APD_{90}, this effect remained modest. Ischaemia-induced shortening of AP duration has been related to the activation of an ATP-sensitive potassium (K-ATP) conductance.[21] The direct effect of morphine on sarcolemmal K-ATP channels in myocytes remains unknown, but recent evidence suggests that mitochondrial K-ATP channels may be opened by opioid receptor stimulation, leading to a preconditioning state.[2 22] Moreover, pretreatment of isolated rat hearts with a selective antagonist of the mitochondrial K-ATP channels abolished the anti-arrhythmic effect of δ_1-opioid receptor stimulation.[2] However, sarcolemmal, but not mitochondrial, K-ATP channels are involved in the repolarization phase of the cardiac AP, supporting the unchanged AP duration reported in our study.

Our study shows that, during simulated myocardial ischaemia, morphine significantly decreased the occurrence of conduction blocks in the border zone. It is well known that slowing of conduction velocity, occurrence of conduction blocks and dispersion of the refractory period between an ischaemic zone and a non-ischaemic zone (‘border zone’) favour the emergence of re-entry arrhythmias.[13 14] This should be considered with the knowledge that morphine is used to treat chest pain associated with myocardial infarction. In contrast, morphine did not modify the occurrence of spontaneous arrhythmias during the ischaemic period, as reported previously.[23 24] However, ischaemia-induced spontaneous arrhythmias are unlikely to be related to re-entry movement because it has been shown that they are independent of stimulation.[7] Although Fryer and colleagues[2] and Wang and colleagues[19] reported an anti-arrhythmic effect of opioid receptor stimulation, in these studies opioid agonists were administered before myocardial ischaemia as triggers of preconditioning.[3 4] In contrast, in our study morphine was administered throughout the duration of ischaemia and reperfusion, as might occur in clinical practice.

Our results show that morphine significantly decreased the incidence of reperfusion-induced repetitive responses around the ‘border zone’ between AZ and NZ. This is in agreement with previous results showing that chronic morphine exposure significantly reduced the incidence and severity of reperfusion-induced arrhythmias in isolated rat hearts.[25] The mechanisms involved in arrhythmias that occur during reperfusion and were morphine-sensitive in our experimental model are not completely understood, but might involve κ-[24] and δ-opioid[2] receptors, adrenoceptor modulation,[26] reduction of conduction block, sodium or calcium overload and possibly reactive oxygen species.[27] The hypothesis of adrenoceptor modulation is supported by studies suggesting that the anti-arrhythmic effect of δ- and κ-opioid receptor stimulation resulted, at least in part, from negative modulation of β-adrenoceptors and a decrease in intracellular calcium oscillations.[26 28] So opioid receptor stimulation may be an important way to counteract the excitatory influence of the sympathetic nervous system, thus preventing dysrrhythmias arising from overactivity of adrenoceptors during ischaemia. Finally, further studies are needed to understand the precise mechanism involved in the anti-arrhythmic effect of morphine in ischaemic—reperfused myocardium.

There are several limitations to our study. First, the simulated ischaemia used modified Tyrode's solution with acidosis, hyperkalaemia, hypoxia and lack of energetic substrates. As described previously,[6 8–11] these conditions accurately reproduced the electrical alterations of cardiac APs observed *in vivo* during experimental myocardial ischaemia.[12] Additionally, the reliability of the double-bath technique is demonstrated by the constancy of the AP parameters in the NZ, adjacent to the AZ. Secondly, the border between normal and ischaemic–reperfused myocardium is probably narrower and more regular than it might be in clinical conditions. As shown previously,[6] this 'border zone' model reproduces arrhythmias similar to those observed *in vivo* during experimental transient coronary artery occlusion[11 12] or in humans during coronary transluminal angioplasty and after thrombolytic therapy.[28] Thirdly, the study was performed on guinea-pig myocardium, which differs from human myocardium, although the main ionic currents involved are qualitatively similar in the two species. Fourthly, the ischaemic conditions used here are severe and did not allow extrapolation of our results to less severe ischaemic insults. Finally, an *in vitro* model, however complex, cannot reproduce the *in vivo* situation exactly but may provide important information for the clinicians.[29]

In conclusion, our study of guinea-pig ventricular muscle shows that clinically relevant concentrations of morphine reduced ischaemia-induced electrophysiological changes, decreased the occurrence of conduction block during simulated ischaemia, and decreased the incidence of reperfusion-induced arrhythmias.

Acknowledgements

This work was supported by the University of Caen

References

1 Mangano DT, Browner WS, Hollenberg M, London MJ, Tubau JF, Tateo IM and the Study of Perioperative Ischemia Research Group. Association of perioperative myocardial ischemia with morbidity and mortality in men undergoing noncardiac surgery. *N Engl J Med* 1990; **323**: 1781–8

2 Fryer RM, Hsu AK, Nagase H, Gross GJ. Opioid-induced cardioprotection against myocardial infarction and arrhythmias: mitochondrial versus sarcolemmal ATP-sensitive channels. *J Pharmacol Exp Ther* 2000; **294**: 451–7

3 Liang BT, Gross GJ. Direct preconditioning of cardiac myocytes via opioid receptors and K_{ATP} channels. *Circ Res* 1999; **25**: 1396–400

4 Bell S, Sack MN, Patel A, Opie LH, Yellon DM. Delta opioid receptor stimulation mimics ischemic preconditioning in human heart muscle *J Am Coll Cardiol* 2000; **36**: 2296–302

5 Gallagher JD. Electrophysiological mechanisms for ventricular arrhythmias in patients with myocardial ischemia: anesthesiologic considerations. Part I. *J Cardiothorac Vasc Anesth* 1997; **11**: 495–505

6 Rouet R, Adamantidis M, Honore E, Dupuis B. *In vitro* abnormal repetitive responses in guinea pig ventricular myocardium exposed to combined hypoxia, hyperkalemia and acidosis. *J Appl Cardiol* 1989; **4**: 19–29

7 Rouet R, Picard S, Libersa C, Ghadanfar M, Albaster C, Gerard JL. Electrophysiological effect of dofetilide in an *in vitro* model of 'border zone' between normal an ischemic/reperfused myocardium. *Circulation* 2000; **101**: 86–93

8 Bellichard P, Pruneau D, Rouet R, Salzmann JL. Electrophysiological responses of hypertrophied rat myocardium to combined hypoxia, hyperkalemia and acidosis. *J Cardiovasc Pharmacol* 1991; **17** (Suppl 2): S141–5

9 Schiariti M, Puddu PE, Rouet R. Multivariate prediction of spontaneous repetitive response in ventricular myocardium exposed *in vitro* to simulated ischemic conditions. *Int J Cardiol* 1994; **45**: 9–22

10 Picard S, Rouet R, Monti F, *et al.* Proarrhythmic effects of DL- and D-sotalol on the 'border zone' between normal and ischemic regions of isolated ventricular myocardium and antiarrhythmic effects on reperfusion. *J Cardiovasc Pharmacol* 1998; **31**: 26–39

11 Morena H, Janse MJ, Fiolet JWT, Krieger WJG, Crijns H, Durrer D. Comparison of the effects of regional ischemia, hypoxia, hyperkalemia and acidosis on intracellular and extracellular potentials and metabolism in isolated porcine heart. *Circ Res* 1980; **46**: 634–46

12 Janse MJ, Cinca J, Morena H, *et al.* The 'border zone' in myocardial ischemia. An electrophysiologial, metabolic and histochemical correlation in pig heart. *Circ Res* 1979; **44**: 576–88

13 Pasnani JS, Ferrier GR. Pro-and anti-arrhythmic effects of D-sotalol and DL-sotalol in an isolated tissue model of ischemia and reperfusion. *J Pharmacol Exp Ther* 1994; **271**: 184–92

14 Janse MJ, Wit AL. Electrophysiological mechanism of ventricular arrhythmias resulting from myocardial ischemia and infarction. *Physiol Rev* 1989; **69**: 1049–169

15 Nawrath H, Rupp J, Jakob H, Sack U, Mertzlufft F, Dick W Failure of opioids to affect excitation and contraction in isolated ventricular heart muscle. *Experientia* 1989; **45**: 337–9

16 Brasch H. Influence of the optical isomers (+)- and (–)-naloxone on beating frequency, contractile force and action potentials of guinea-pig isolated cardiac preparations. *Br J Pharmacol* 1986; **88**: 733–40

17 Hung CF, Tsai CH, Su MJ. Opioid receptor independent effects of morphine on membrane currents in single cardiac myocytes. *Br J Anaesth* 1998; **81**: 925–31

18 Sarton E, Olofsen E, Romberg R, *et al.* Sex differences in morphine analgesia: an experimental study in healthy volunteers. *Anesthesiology* 2000; **93**: 1245–54

19 Wang GY, Wu S, Pei JM, Yu XC, Wong TM. κ- but not δ-opioid

receptors mediate effects of ischemic preconditioning on both infarct and arrhythmia in rats. *Am J Physiol* 2001; **280**: H384–91

20 Sarne Y, Flitstein A, Oppenheimer E. Anti-arrhythmic activities of opioid agonists and antagonists and their stereoisomers. *Br J Pharmacol* 1991; **102**: 696–8

21 Coetzee WA. ATP-sensitive potassium channels and myocardial ischemia: why do they open? *Cardiovasc Drug Ther* 1992; **6**: 201–8

22 Cohen MV, Yang XM, Liu GS, Heusch G, Downey JM. Acetylcholine, bradykinin, opioids, and phenylephrine, but not adenosine, trigger preconditioning by generating free radicals and opening mitochondrial K(ATP) channels. *Circ Res* 2001; **89**: 273–8

23 Murphy DB, Murphy MB. Opioid antagonist modulation of ischaemia-induced ventricular arrhythmias: a peripheral mechanism. *J Cardiovasc Pharmacol* 1999; **33**: 122–5

24 Yu XC, Wang HX, Pei JM, Wong TM. Anti-arrhythmic effect of k-opioid receptor stimulation in the perfused rat heart: involvement of a cAMP-dependent pathway. *J Mol Cell Cardiol* 1999; **31**: 1809–19

25 Wong TM, Lee AY. Chronic morphine treatment reduces the incidence of ventricular arrhythmias in the isolated rat heart induced by dynorphin 1–13 or myocardial ischemia and reperfusion *Neurosci Lett* 1987; **77**: 61–5

26 Pepe S, Xiao RP, Hohl C, Altschuld R, Lakatta EG. Cross talk between opioid peptide and adrenoceptor signaling in isolated rat heart. *Circulation* 1997; **95**: 2122–9

27 Corr PB, Witowski FX. Potential electrophysiologic mechanisms responsible for dysrrhythmias associated with reperfusion of ischemic myocardium. *Circulation* 1983; **68**: 16–24

28 Tzivoni D, Keren A, Granot H, Gottlieb S, Benhorin J, Stern S Ventricular fibrillation caused by myocardial reperfusion in Printzmetal angina. *Am Heart J* 1983; **105**: 323–5

29 Rosen MR. The links between basic and clinical cardiac electrophysiology *Circulation* 1988; **77**: 251–63

British Journal of Anaesthesia **89** (6): 896–903 (2002)

Sevoflurane preconditions stunned myocardium in septic but not healthy isolated rat hearts

R. Serita, H. Morisaki*, K. Ai, Y. Morita, Y. Innami, T. Satoh, S. Kosugi, Y. Kotake and J. Takeda

Department of Anaesthesiology and General Intensive Care Unit, Keio University School of Medicine, Tokyo 160-8582, Japan

**Corresponding author. E-mail: anesmrsk@sc.itc.keio.ac.jp*

Background. Recent evidence indicates that sevoflurane treatment before prolonged ischaemia reduces infarct size in normal hearts, mimicking ischaemic preconditioning. We examined whether exposure to sevoflurane before brief ischaemia, inducing a 'stunned myocardium', provided such protective effects in an isolated working heart from normal or septic rats.

Methods. With institutional approval, 91 rats were randomly allocated into one of either caecal-ligation and perforation (CLP: *n*=50) or sham (Sham: *n*=41) procedure groups 24 h before the study. After determination of baseline measurements, including cardiac output (CO), myocardial oxygen consumption ($m\dot{V}O_2$) and cardiac efficiency (CE; CO×peak systolic pressure/$m\dot{V}O_2$), each isolated heart was perfused with or without 2% sevoflurane for 15 min before global ischaemia (pre-ischaemia). After 15 min ischaemia and 30 min reperfusion, all hearts were assessed for functional recovery of myocardium (post-reperfusion).

Results. During the pre-ischaemia period, 2% sevoflurane caused a significant reduction of CO in the CLP group compared with the Sham group. During the post-reperfusion period, both CO (16.9 *vs* 11.0 ml min^{-1}) and CE (11.2 *vs* 7.7 mm Hg ml^{-1} $(\mu l\ O_2)^{-1}$) was higher in the sevoflurane-treated *vs* -untreated hearts from CLP rats, and was accompanied by lower incidence of reperfusion arrhythmia compared with control hearts (8 *vs* 32%). In contrast, 2% sevoflurane did not provide cardioprotective effects in normal rats.

Conclusions. The current study demonstrates that pre-treatment with sevoflurane minimizes myocardial dysfunction and the incidence of reperfusion arrhythmia after brief ischaemic insults in septic hearts.

Br J Anaesth 2002; **89**: 896–903

Keywords: anaesthetics volatile, sevoflurane; heart, reperfusion arrhythmia; infection, sepsis

Accepted for publication: July 23, 2002

Several pharmacological agents such as adenosine and opioids have been shown to produce similar properties to ischaemic preconditioning, defined as the concept that repeated short periods of ischaemia render the heart more resistant to a subsequent sustained ischaemic period.[1–3] Recently, an increasing amount of evidence indicated that exposure to volatile anaesthetics also displays protective roles on ischaemic myocardium, mimicking such ischaemic preconditioning.[4–6] For example, in dogs, sevoflurane treatment before ischaemia reduced infarct size, possibly through the opening of adenosine triphosphate-sensitive potassium (K_{ATP}) channels.[7] Compared with other volatile anaesthetics, sevoflurane is characterized by the preservation of myocardial blood flow through the involvement of collateral circulation, independent of K_{ATP} channels.[8 9] However, it remains unclear whether such properties of sevoflurane work in stunned myocardium, that is transient myocardial dysfunction after short periods of ischaemia.

Sepsis, characterized by a marked elevation of tissue oxygen demand, is frequently accompanied by multiple organ failure including myocardial dysfunction even at the early stage of the hyperdynamic circulatory state.[10 11] A previous study showed that the ultra-structural architecture of the myocardium, including mitochondria and myofibrils, were swollen and damaged in a large animal model of sepsis.[12] Thus, septic myocardium may not be able to utilize oxygen efficiently even under the conditions of supranormal oxygen supply to the myocardium.[11] In addition, another

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

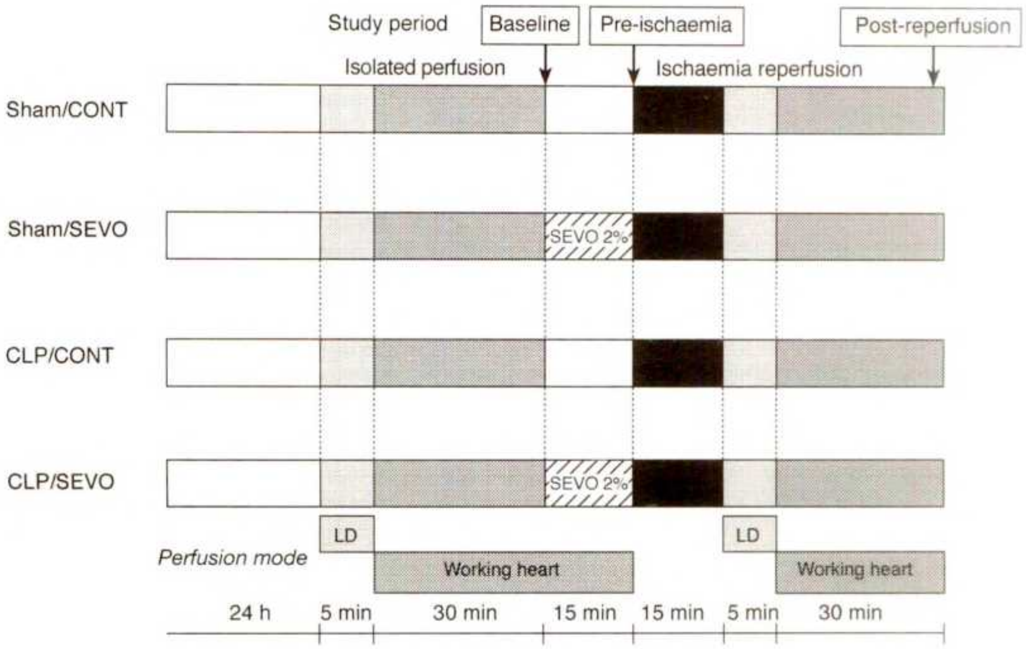


Fig 1 Schematic drawing of experimental procedure. Abbreviations: Sham, Sham group; CLP, caecal-ligation and perforation group; CONT, control group; SEVO, sevoflurane group; LD, Langendorff's retrograded perfusion mode.

study demonstrated that the flow reserve of the coronary circulation to maximize blood flow and oxygen extraction was limited.[13] Thus, septic myocardium appears to be more vulnerable to even brief periods of ischaemia and subsequent reperfusion. We, therefore, tested the hypothesis that sevoflurane protected the septic heart from ischaemia to produce a 'stunned myocardium'. In the present study, we used the caecal-ligation and perforation (CLP) model to develop the early stage of sepsis as described previously.[14] Using an isolated working heart from CLP-treated rats, we examined whether exposure of 2% sevoflurane served to minimize myocardial dysfunction and the incidence of reperfusion arrhythmia following brief period of ischaemia.

Materials and methods

This study procedure was approved by the animal care and utilization committee in Keio University School of Medicine.

Animal preparation

Ninety-one male Wistar rats, weighing 310–380 g, were studied after a 3- to 7-day period of acclimatization in our laboratory. Water and laboratory chow were available *ad libitum* after intraperitoneal (i.p.) injection of pentobarbital (30 mg kg^{-1}) and the femoral vein was cannulated with a catheter (PE50; Intermedic, Sparks, MD, USA) under sterile conditions. The animals were then randomized into either sham-treatment (Sham) or CLP group. In the latter animals, a laparotomy was performed and a ligature was placed around the caecum immediately distal to the ileocaecal valve. The caecum was then punctured twice with an 18-gauge needle. Following this preparatory surgery, normal saline was infused at 3 ml h^{-1} via the catheter for the next 24 h. This preparation was demonstrated to produce normotensive, hyperdynamic sepsis.[14] As the laparotomy *per se* caused septic responses in rats, the Sham animals in this experiment did not receive open laparotomy as described previously.[15]

Study procedure

Figure 1 depicts the study procedure. Twenty-four hours after randomization to either the Sham (n=41) or CLP (n=50) group, animals were anaesthetized with sevoflurane in oxygen. After the intravenous (i.v.) injection of heparin (300 IU kg^{-1}), the abdomen was opened and 1 ml of blood was taken from descending aorta for subsequent analyses of arterial lactate. Thereafter, the hearts were rapidly excised, mounted on a non-recirculating Langendorff apparatus to allow further preparation, and perfused with modified Krebs–Henseleit solution at 37°C (composition in mM: NaCl 120, KCl 4.8, KH_2PO_4 1.2, $MgSO_4$ 1.2, $CaCl_2$ 1.25, $NaHCO_3$ 25, and glucose 11) as described previously.[5] The perfusion buffer was equilibrated with a 95% oxygen/5% carbon dioxide gas mixture, resulting in a buffer P_{O_2} above 60 kPa.

Spontaneous beating hearts were used throughout the study periods. Following aortic cannulation, the left atrium was cannulated through the pulmonary vein to allow filling and contraction of the left atrium. With the left atrial cannula open, the Langendorff column was closed and the aortic outflow line opened so that buffer entering through the left atrium could be pumped out of the left ventricle, that is the antegrade working mode. As perfusion of left atrium provided sufficient heart rate in this mode, electrical pacing was obviated to examine the protective effects of sevoflurane on reperfusion arrhythmia. During this working mode, a left atrial filling pressure of 15 cm H_2O and a mean aortic pressure of 70 cm H_2O were maintained by adjusting the height of the left atrial buffer reservoir above the heart and by a column height equivalent to 70 cm H_2O, respectively. Following ligation of the superior and inferior vena cava in addition to the pulmonary veins to ensure that the coronary effluent passed through the pulmonary artery, the pulmonary artery was cannulated with 16-gauge steel cannula and right ventricular outflow was monitored with transit-time ultrasound flowmeter (T206, Transonic Systems Inc., New York, USA) for the measurement of coronary flow as described previously.[16 17] The probe of this flowmeter was also attached to the aortic flow root. Simultaneously, a catheter-tip pressure transducer (post-craniotomy subdural pressure monitoring kit; 110-4G, Neuro Care Group Camino, CA, USA) was inserted into the left ventricle through the left atrium.

After 30 min of initial perfusion in working mode, baseline measurements were used. The hearts were further randomized into two subgroups: control or sevoflurane group. The latter subgroup (Sham/SEVO, *n*=20 or CLP/SEVO, *n*=25) was perfused for 15 min with modified Krebs–Henseleit solution, in which sevoflurane was administered at 2.0% via a calibrated sevoflurane vaporizer (Datex-Ohmeda, Helsinki, Finland). Control hearts were subjected to the same perfusion procedure without administration of sevoflurane (Sham/CONT, *n*=21 or CLP/CONT, *n*=25). All isolated perfused hearts underwent 15 min global ischaemia at room temperature (approximately 25°C). The hearts were then re-perfused for 5 min in a Langendorff's perfusion mode, followed by working heart mode at 37°C for 30 min without sevoflurane. As depicted in Figure 1, measurements described below were repeated during the pre-ischaemic and post-reperfusion periods. Hearts were immediately freeze-clamped between blocks of metal cooled to the temperature of liquid nitrogen and stored at –40°C until extraction for high-energy phosphate analyses.

Specific measurements and calculations

Cardiac output (CO) was defined as the sum of coronary and aortic flows in this experimental setting as described previously.[16] Left-ventricular pressure (LVP) was continuously monitored with a transducer (post-craniotomy subdural pressure monitoring kit; 110-4G, Neuro Care Group Camino, CA, USA and Life Scope II, Nihon Koden, Tokyo, Japan) and recorded in a digital recorder (PC208, Sony, Tokyo, Japan). Using computer software (Acqknowledge v3.0 data acquisition systems, Biopac Systems, Goleta, CA, USA and Microsoft Excel, Microsoft, WA, USA), LV peak systolic pressure (LVPSP), LV end-diastolic pressure (LVEDP), maximum rate of LV pressure rise (dP/dt_{max}), and heart rate (HR) were calculated, based on the averages of five beats. LV developed pressure (LVDP), which was regarded as a marker of contractility of the isolated rat heart, was calculated by subtracting LVEDP from LVPSP.[17] Reperfusion arrhythmia was defined as the irregular intervals of peak systolic pressure on the pressure monitor 5 min after the initiation of working mode.

P_{O_2} of the perfusion medium obtained at pre-perfusion (in-flow) and right ventricular outflow (out-flow) was determined using a standard blood gas analyser (Chiron 860 series, Chiron Diagnostics Corp., East Walpole, MA, USA). Oxygen delivery was calculated as inflow oxygen tension, in millimetres of mercury, multiplied by oxygen solubility (24 µl ml^{-1} Krebs–Ringer's solution at 760 mm Hg oxygen and 37°C) and coronary flow (ml min^{-1}). Myocardial oxygen consumption ($m\dot{V}O_2$) was calculated as oxygen solubility multiplied by the difference between in-flow and out-flow oxygen tension and coronary flow. CE was determined as the ratio of cardiac work, the product of CO (ml min^{-1})×LVPSP (mm Hg), to $m\dot{V}O_2$ uncorrected for heart weight as described previously.[18 19]

Biochemical analyses

High-energy phosphates in the myocardium were measured as described previously.[20] Briefly, freeze-clamped left ventricular tissue from CLP and Sham animals were first broken in a frozen sample crusher (TK-CM20S, Yaghi Grassware, Tokyo, Japan) and then homogenized with a teflon-coated homogenizer (Iuchi, Tokyo, Japan) in ice-chilled 0.6 N perchloric acid. The samples were centrifuged (3000 *g* for 10 min), neutralized with 1 N potassium hydroxide, and re-centrifuged. Myocardial creatine phosphate (CrP), adenosine monophosphate (AMP), adenosine diphosphate (ADP), and adenosine triphosphate (ATP) contents were measured using high-performance liquid chromatography with a reverse-phase column (Shim-Pack VP-ODS, Shimazu, Tokyo, Japan). Elution was performed at 1.0 ml min^{-1}, and an ultraviolet/visible spectrophotometer (Shimazu, SPD-10A, Tokyo, Japan) at 210 nm was used to detect these phosphates. Tissue contents of these metabolites were reported in micromoles per gram wet tissue.

Statistical analysis

This experiment utilized a three-factor design with a full 2×2 factorial allotment to (CLP/Sham)×(CONT/SEVO). The third factor, ischaemia-reperfusion, was implemented as a repeated measure. Values are described as mean (SD) unless otherwise specified. To compare and contrast the effects of sepsis across the sevoflurane treatment groups before the induction of ischaemia-reperfusion, two-way analysis of variance was employed using a statistical

Table 1 Baseline myocardial function in the Sham and CLP groups at the baseline stage. Data were expressed as mean (SD). Significance: $^*P<0.01$ *vs* Sham group

Group	LVDP (mm Hg)	LVEDP (mm Hg)	dP/dt_{max} (mm Hg s^{-1})	CO (ml min^{-1})	Heart rate (beats min^{-1})	Stroke volume (ml)	Coronary flow (ml min^{-1})
Sham	89.8 (11.3)	7.8 (3.1)	2610 (470)	48.9 (9.9)	292 (54)	0.17 (0.04)	13.4 (2.1)
CLP	77.7 (14.1)*	7.9 (3.0)	2020 (500)*	32.6 (1.3)*	253 (58)*	0.13 (0.05)*	10.7 (2.2)*

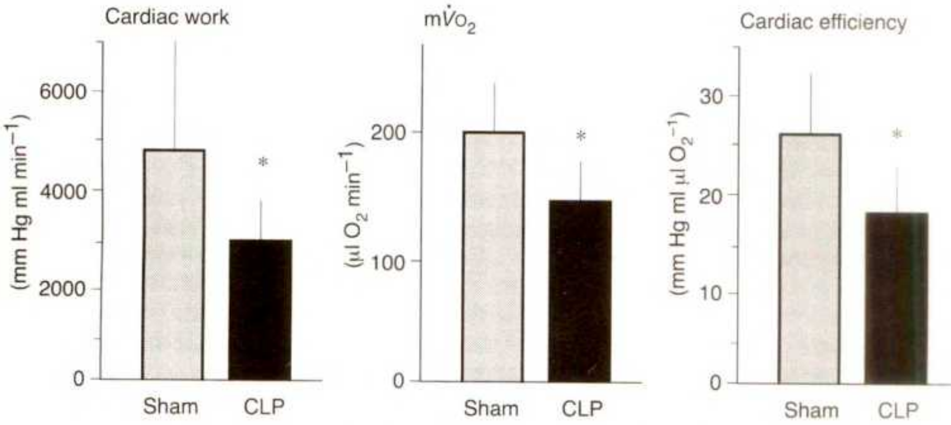


Fig 2 Baseline differences of myocardial function in an isolated working heart between Sham and CLP rats. Abbreviations: Sham, Sham group; CLP, caecal-ligation and perforation group; m$\dot{V}o_2$, myocardial oxygen consumption. Cardiac efficiency, the ratio of cardiac work, the product of CO×LVPSP, to m$\dot{V}o_2$. Significance: $^*P<0.05$ *vs* Sham group.

package of SPSS/9.0J for Windows (SPSS Inc., Chicago, IL, USA). After induction of ischaemia-reperfusion, results between baseline and post-reperfusion periods were analysed using repeated-measures analysis of variance. Where appropriate, directed pair-wise comparisons of individual groups were conducted using a Bonferroni-corrected 95% confidence interval. The incidence of arrhythmia was examined using Kruskal–Wallis test. A P value <0.05 was regarded as significant.

Results

Sepsis model and myocardial function in vitro

At 24 h after laparotomy, all CLP rats demonstrated reduced activity, pilo-erection and exudation around eyes and nose. At postmortem, pan-peritonitis with moderate volume of ascites was confirmed in all CLP rats. Arterial lactate levels were not significantly different 24 h after CLP [2.0 (0.5) *vs* 2.6 (1.1) mmol litre^{-1}]. In contrast, sham-treated animals demonstrated an uneventful recovery from anaesthesia and had no marked sign of illness. As no significant differences were found within each major group at baseline, individual data were pooled into either the CLP or Sham group as shown in Table 1. Baseline haemodynamic values, including LVDP, dP/dt_{max}, and CO, along with both HR and stroke volume, were significantly lower in the CLP group than those in the Sham group ($P<0.01$), whereas LVEDP was similar between the groups. Simultaneously, the coronary flow was depressed to approximately 80% of the Sham animals in the CLP group. Figure 2 shows baseline differences of cardiac work, m$\dot{V}o_2$ and cardiac efficiency between the Sham and CLP. Compared with normal, septic hearts from the CLP rats showed not only significantly less work and oxygen consumption but also less efficiency over the baseline study period.

Effects of sevoflurane in normal or septic heart against ischaemia-reperfusion

Table 2 illustrates the time course of myocardial function throughout the study periods with or without sevoflurane pre-treatment in the hearts of Sham and CLP rats. In the Sham group, no differences in myocardial function were observed at the baseline between CONT and SEVO subgroups. Although the difference of LVDP at pre-ischaemia was not statistically significant, a reduction of dP/dt_{max} and approximately a 28% decrease of CO with constant heart rates in the SEVO subgroup were found. Two per cent sevoflurane decreased mainly stroke volume in an isolated working mode of normal rat heart. In contrast, both m$\dot{V}o_2$ and coronary flow did not change during sevoflurane exposure. With ischaemia and reperfusion, all parameters of myocardial function including LVDP, dP/dt_{max}, and CO were significantly depressed, and were accompanied by a reduction of m$\dot{V}o_2$ and coronary flow, indicating that a 'stunned myocardium' developed in this experimental setting. Alternatively, sevoflurane exposure before 15 min

Table 2 Changes of haemodynamic parameters of working heart model in Sham and CLP groups with or without sevoflurane treatment. Data were expressed as mean (SD). Abbreviations: CONT, no treatment; SEVO, sevoflurane treatment. Significance: *$P<0.05$, **$P<0.01$ *vs* CONT group, $^{\dagger}P<0.05$, $^{\ddagger}P<0.01$ *vs* the baseline period

	Group	Subgroup	Baseline	Pre-ischaemia	Post-reperfusion
LVDP (mm Hg)	Sham	CONT	91.4 (9.2)	86.9 (6.2)	73.7 (12.9)†
		SEVO	88.1 (13.3)	81.4 (13.8)	75.3 (13.7)†
	CLP	CONT	80.0 (14.1)	77.0 (10.0)	67.9 (12.3)
		SEVO	75.6 (14.2)	71.1 (13.2)	69.7 (13.4)
LVEDP (mm Hg)	Sham	CONT	7.7 (3.1)	7.7 (3.4)	8.5 (3.4)
		SEVO	7.9 (3.0)	7.9 (2.7)	8.4 (2.9)
	CLP	CONT	8.2 (2.9)	8.4 (2.9)	9.1 (3.1)
		SEVO	7.6 (3.3)	8.1 (3.2)	9.4 (3.2)
dP/dt_{max} (mm Hg s^{-1})	Sham	CONT	2570 (520)	2520 (410)	1960 (360)†
		SEVO	2650 (440)	2240 (360)*	2020 (540)†
	CLP	CONT	2090 (420	2000 (370)	1640 (470)
		SEVO	1970 (560)	1810 (550)	1710 (500)
CO (ml min^{-1})	Sham	CONT	48.9 (8.4)	46.8 (9.3)	23.5 (9.9)‡
		SEVO	48.9 (11.5)	33.7 (12.4)†**	25.1 (11.2)‡
	CLP	CONT	31.9 (9.9)	32.1 (8.4)	11.0 (6.1)‡
		SEVO	33.2 (12.7)	22.2 (7.8)‡**	16.9 (6.3)†*
Heart rate (beats min^{-1})	Sham	CONT	296 (60)	304 (60)	267 (65)
		SEVO	288 (48)	275 (60)	281 (63)
	CLP	CONT	256 (46)	262 (44)	236 (33)
		SEVO	250 (68)	244 (66)	229 (58)
m$\dot{V}\text{O}_2$ (µl min^{-1})	Sham	CONT	200 (36)	190 (36)	148 (33)†
		SEVO	198 (48)	174 (45)	143 (41)†
	CLP	CONT	160 (39)	155 (39)	120 (33)†
		SEVO	170 (41)	163 (44)	124 (33)†
Coronary flow (ml min^{-1})	Sham	CONT	13.5 (2.0)	13.1 (2.3)	9.2 (2.2)†
		SEVO	13.2 (2.3)	12.3 (2.5)	9.3 (2.2)†
	CLP	CONT	10.5 (2.1)	10.1 (1.9)	7.7 (1.9)†
		SEVO	10.9 (2.3)	10.5 (2.4)	7.5 (2.0)†

ischaemia caused no significant changes in myocardial function after reperfusion compared with those without sevoflurane treatment. In contrast, in CLP rats, exposure of 2% sevoflurane for 15 min caused a significant depression of CO without changes in LVDP, dP/dt_{max}, or HR (Table 2). Both coronary blood flow and m$\dot{V}\text{O}_2$ were preserved during sevoflurane exposure as observed in the Sham group. After reperfusion, sevoflurane treatment minimized the depression of CO compared with CLP/CONT group. Other parameters of myocardial function in the SEVO subgroup showed comparable changes with the CONT group. Simultaneously, coronary blood flow and m$\dot{V}\text{O}_2$ were not significantly different between the two subgroups, whereas they were decreased from baseline in both subgroups. Collectively, the data suggest that sevoflurane modified neither m$\dot{V}\text{O}_2$ nor coronary blood flow of septic hearts after reperfusion.

There was no significant difference in the incidence of reperfusion arrhythmia between the sevoflurane-treated and -untreated rats (25 *vs* 10%) in the Sham group. In contrast, in CLP rats this was significantly reduced with sevoflurane treatment compared with non-treated rats (8 *vs* 32%, respectively, $P=0.027$). Figure 3 shows the differences in cardiac work, m$\dot{V}\text{O}_2$ and cardiac efficiency with or without sevoflurane treatment in the Sham and CLP groups during the post-reperfusion period. All parameters in the CLP group, but not m$\dot{V}\text{O}_2$ with sevoflurane treatment, were significantly lower than those in the Sham group. Both cardiac work and m$\dot{V}\text{O}_2$ were not different irrespective of the presence of sevoflurane in the Sham or CLP groups. However, sevoflurane provided better cardiac efficiency, that is, more efficient oxygen utilization to cardiac work, in the CLP group, whereas this was not significantly different between sevoflurane-treated and -untreated animals in the Sham group.

Changes in myocardial high-energy phosphates

The effects of sepsis and a brief period of sevoflurane exposure on myocardial high-energy phosphates were examined at the end of the study procedure (Table 3). Myocardial high-energy phosphates such as ATP, ADP, and AMP were not modulated significantly by CLP or sevoflurane exposure during the post-reperfusion period.

Discussion

The present study indicates that brief exposure to 2% sevoflurane before ischaemic insult to induce 'myocardial stunning' provides protective effects in sepsis. Although such effects of sevoflurane were obvious in the preservation of CO, this parameter, consisting of both contractility and heart rate, was likely to represent myocardial performance rather than LVDP or dP/dt *per se* under a constant afterload. In addition, cardiac efficiency was better preserved after reperfusion in sevoflurane-treated *vs* -untreated septic hearts

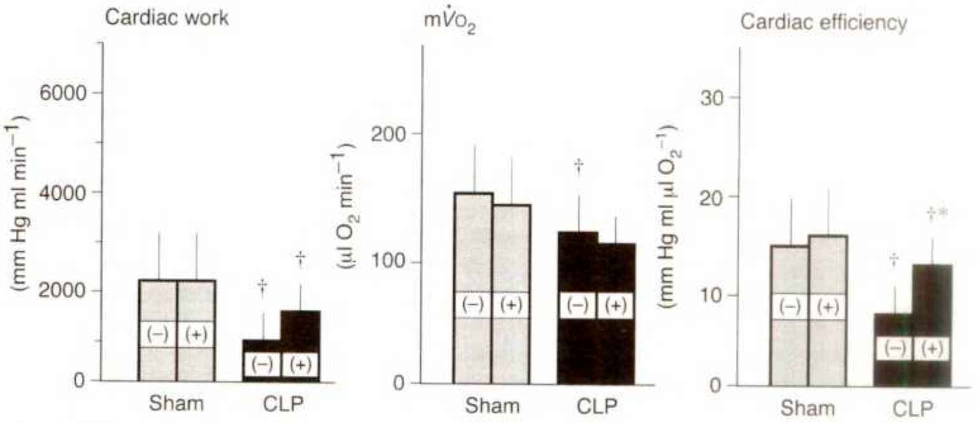


Fig 3 Effects of sevoflurane treatment on myocardial function in an isolated working heart in both Sham and CLP groups during the post-reperfusion period. Abbreviations: Sham, Sham group; CLP, caecal-ligation and perforation group; m$\dot{V}O_2$, myocardial oxygen consumption. Cardiac efficiency, the ratio of cardiac work, the product of CO×LVPSP, to m$\dot{V}O_2$. Significance: †$P<0.05$ *vs* Sham group, *$P<0.05$ *vs* sevoflurane untreated subgroup.

Table 3 Myocardial high-energy phosphate contents at the end of reperfusion. Data were standardized as µmol (g wet-tissue weight)$^{-1}$ and expressed as mean (SD). Abbreviations: CONT, no treatment; SEVO, sevoflurane treatment

Group	Subgroup	ATP	ADP	AMP	CrP
Sham	CONT	0.51 (0.15)	0.90 (0.46)	0.56 (0.35)	0.87 (0.58)
	SEVO	0.54 (0.35)	0.72 (0.20)	0.51 (0.27)	0.70 (0.51)
CLP	CONT	0.45 (0.17)	0.72 (0.21)	0.54 (0.21)	1.43 (0.94)
	SEVO	0.41 (0.23)	0.65 (0.13)	0.48 (0.18)	0.51 (0.42)

(Fig. 3). Thus, sevoflurane treatment improved oxygen utilization of myocardium to achieve a certain level of cardiac work after brief ischaemia in septic hearts. Another important finding of the present study was that sevoflurane pre-treatment reduced the incidence of reperfusion arrhythmia in septic hearts perfused in a working mode. Therefore, sevoflurane treatment preserves not only contractility but also other profiles of myocardial function including electrical conductance in septic hearts after ischaemia and reperfusion through the improvement of oxygen metabolism.

Whilst previous studies showed that exposure to volatile anaesthetics protected healthy myocardium from prolonged 'irreversible' ischaemia by assessing the reduction of infarct size, there were conflicting results as to whether similar profiles could be given to 'reversible' myocardial injury, that is stunned myocardium.[7 21] Indeed, sevoflurane treatment in this experimental condition did not show any cardioprotective properties against ischaemia-reperfusion injury in healthy hearts. There are several possibilities to account for such a discrepancy between the present and previous studies. First, sevoflurane concentration might not be high enough to obtain its preconditioning-like effects in healthy hearts. Previous studies demonstrated that the minimum alveolar concentration (MAC) of sevoflurane was significantly reduced from 2.4 to 1.35% level in a porcine model of sepsis.[22] Another study using the same CLP-rat model also showed that the MAC required for isoflurane was lowered to a similar extent.[23] Given these findings, it is not unreasonable to consider that the potency of anaesthetics on the isolated myocardium is different between the Sham and CLP groups. If equipotent sevoflurane doses were given to each group, this might have protected the healthy heart from ischaemia–reperfusion injury to cause stunned myocardium. Indeed, it should be noted that there are conflicting results, possibly caused by different concentrations of anaesthetic agents exposed at different time periods among previous studies.[5 9 24 25] Secondly, sevoflurane anaesthesia for the excision of hearts might have already provided preconditioning-like effects even in the control hearts. Although sevoflurane is much less likely to remain *in situ* after reperfusion compared with other anaesthetics because of its lower blood–gas solubility,[26] this possibility could not be fully excluded. On the other hand, the study design to terminate sevoflurane treatment during the reperfusion period could have modified its cardioprotective effects in healthy hearts. Thirdly, ischaemic insults to evoke a stunned myocardium in the present study might not be severe enough to show distinct protective effects of sevoflurane in health where myocardial reserve is more sufficient than in sepsis.[11] In other words, if a longer period of ischaemia was applied to this model, protection might have been unmasked. Furthermore, hypothermic global ischaemia as we applied could be another factor to reduce the severity of the ischaemia–reperfusion injury compared with normothermic ischaemia as described elsewhere.[16 17]

Despite the instability of this septic challenge, the CLP model with fluid resuscitation has been considered most relevant to the early stage of sepsis, concomitantly obviating confounding factors like hypotension.[12 14 27] In accordance with these findings, we found no significant elevation of arterial lactate 24 h after CLP, indicating that tissue hypoxia was not evident in this model of sepsis. Even under such conditions, both myocardial contractility, expressed as LVDP, dP/dt_{max} and CO, and heart rate in the CLP group were significantly lower compared with the Sham group at baseline (Table 1), suggesting that not only inotropic but also chronotropic properties synergistically serve in the development of myocardial dysfunction in sepsis. However, it should also be noted that CO was significantly depressed in the early stage of sepsis under a constant afterload in this isolated preparation. Furthermore, the present study shows that $m\dot{V}O_2$ is significantly depressed *ex vivo* with the reduction in coronary flows and CO (Table 1) whereas it is unknown whether $m\dot{V}O_2$ in the hyperdynamic state of sepsis is indeed augmented or not. A previous study demonstrated that pro-inflammatory cytokines, released in sepsis, depressed myocardial function accompanied by reduction of $m\dot{V}O_2$ through nitric oxide-dependent mechanisms.[18] Further investigations are required to clarify this issue.

Neither CLP nor sevoflurane exposure appears to modify myocardial energy levels, indicating that improved high-energy phosphate contents were not singularly important determinants of post-ischaemic ventricular function. Support for this contention was provided by previous studies, which demonstrated the dissociation between ventricular function and ATP levels in post-ischaemic hearts.[28 29] Some investigations showed that myocardial high-energy phosphates content correlated neither with myocardial dysfunction in sepsis nor with cardioprotection by ischaemic preconditioning.[30 31] Collectively, one possibility could be raised that the significant reduction in CO, accompanied by depressed $m\dot{V}O_2$, resulted in stored high-energy phosphates in the CLP group more than those in the Sham group, subsequently preserving the amount of ATP contents in the CLP group. Furthermore, both a reduction of cardiac efficiency and no changes of myocardial high-energy phosphates in the CLP group, indicates a possibility that sepsis reduces the ability of the myocardium to utilize high-energy phosphates for contractile work, but not inhibit mitochondrial respiration. Nevertheless, the current results provide evidence that energy utilization in the septic heart is augmented with treatment of sevoflurane before ischaemia.

There are several limitations to this study. First, despite a physiologically correct direction of perfusion, the isolated working model limits the evaluation of data regarding myocardial function in sepsis. For example, humoral factors like cytokines and circulating inflammatory cells such as leukocytes or platelets, both of which play consequential roles in the development of sepsis, are excluded from the perfusion medium in this study design. Furthermore, because of constant afterload and depressed contractility, the augmentation of CO observed in this early stage of sepsis was not found during the baseline period. Secondly, it could be argued that myocardial function could be evaluated more accurately if the heart rates were kept constant. Contrary to Langendorff mode, however, sufficient heart rate could be obtained in an isolated working heart because of perfusion to left atrium as described previously.[19] In addition, under pacing conditions this model could lose the effects of sevoflurane on heart rates, subsequently modifying CO. Finally, the isolation procedure *per se* may be able to ischaemic-precondition the heart, possibly modifying the outcome. However, as we performed the study in the same manner by a single investigator in random, we believe that the data were comparable at least between the groups.

In conclusion, the current study shows that sevoflurane provides protective effects, in septic but not healthy hearts, against brief ischaemic insults through the improvement of myocardial oxygen utilization. Further investigation is warranted to elucidate whether other anaesthetic preconditioning protects the myocardium against brief or prolonged period of ischaemia 'in diseased hosts'.

Acknowledgements

This investigation was supported by the Grants-in-Aid for the Scientific Research from the Ministry of Education, Science and Culture, Tokyo.

References

1 Yao Z, Gross GJ. A comparison of adenosine-induced cardioprotection and ischemic preconditioning in dogs. Efficacy, time course, and role of K_{ATP} channels. *Circulation* 1994; **89**: 1229–36

2 Schultz JEJ, Hsu AK, Gross GJ. Morphine mimics the cardioprotective effect of ischemic preconditioning via a glibenclamide-sensitive mechanism in the rat heart. *Circ Res* 1996; **76**: 1100–4

3 Baxter GB. Ischemic preconditioning of myocardium. *Ann Med* 1997; **29**: 345–52

4 Cason BA, Gamperl AK, Locum RE, Hickey RF. Anesthetic-induced preconditioning. Previous administration of isoflurane decreases myocardial infarct size in rabbits. *Anesthesiology* 1997; **87**: 1182–90

5 Coetzee JF, le Roux PJ, Genade S, Lochner A. Reduction of postischemic contractile dysfunction of the isolated rat heart by sevoflurane: comparison with halothane. *Anesth Analg* 2000; **90**: 1089–97

6 Preckel B, Schlack E, Comfère T, Obal D, Barthel H, Thämer V. Effects of enflurane, isoflurane, sevoflurane and desflurane on reperfusion injury after regional myocardial ischaemia in the rabbit heart *in vivo*. *Br J Anaesth* 1998; **81**: 905–12

7 Toller WG, Kersten JR, Pagel PS, Hettrick DA, Warltier DC. Sevoflurane reduces myocardial infarct size and decreases the time threshold for ischemic preconditioning in dogs. *Anesthesiology* 1999; **91**: 1437–46

8 Kersten JR, Brayer AP, Pagel PS, Tessmer JP, Warltier DC. Perfusion of ischemic myocardium during anesthesia with sevoflurane. *Anesthesiology* 1994; **81**: 995–1004

9 Kersten JR, Schmeling T, Tessmer J, Hettrick DA, Pagel PS, Warltier DC. Sevoflurane selectively increases coronary

collateral blood flow independent of K_{ATP} channels *in vivo*. *Anesthesiology* 1999; **90**: 246–56

10 Members of American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee. Definition for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992; **20**: 864–74

11 Abel FL Myocardial function in sepsis and endotoxic shock *Am J Physiol* 1989; **257**: R1265–81

12 Morisaki H, Bloos F, Keys, Martin C, Neal A, Sibbald WJ. Compared to crystalloid, colloid therapy slows progression of extrapulmonary tissue injury in septic sheep. *J Appl Physiol* 1994; **77**: 1507–18

13 Bloos F, Morisaki H, Neal A, Martin CM, Ellis CG, Sibbald WJ. Sepsis depresses the metabolic oxygen reserve of the coronary circulation in mature sheep. *Am J Respir Crit Care Med* 1996; **153**: 1577–84

14 Morisaki H, Sibbald W, Martin C, Doig G, Inman K. Hyperdynamic sepsis depresses circulatory compensation to normovolemic anemia in conscious rats. *J Appl Physiol* 1996; **80**: 656–64

15 Piper RD, Li FY, Myers ML, Sibbald WJ. Effects of isoproterenol on myocardial structure and function in septic rats. *J Appl Physiol* 1999; **86**: 993–1001

16 Novalija E, Fujita S, Kampire JP, Stowe DF. Sevoflurane mimics ischemic preconditioning effects on coronary flow and nitric oxide release in isolated hearts. *Anesthesiology* 1999; **91**: 701–12

17 Ismail JA, McDonough KH The role of coronary flow and adenosisne in postischemic recovery of septic rat hearts *Am J Physiol* 1998; **275**: H8–14

18 Panas D, Khadour FH, Szabo C, Schulz R. Proinflammatory cytokines depress cardiac efficiency by a nitric oxide-dependent mechanism. *Am J Physiol* 1998; **275**: H1016–23

19 Taniguchi M, Wilson C, Hunter CA, Pehowich DJ, Clanachan AS, Lopaschuk GD. Dichloroacetate improves cardiac efficiency after ischemia independent of changes in mitochondrial protein leak. *Am J Physiol* 2001; **280**: H1762–9

20 Headrick JP, Dobson GP, Williams JP, McKirdy JC, Jordan L, Willis RJ. Bioenergetics and control of oxygen consumption in the *in situ* rat heart. *Am J Physiol* 1994; **267**. H1074–84

21 Sheridan DJ, Penkoske PA, Sobel BE, Corr PB Alpha adrenergic contributions to dysarrhythmia during myocardial ischemia and reperfusion in cats. *J Clin Invest* 1980; **65**: 161–71

22 Allaouchiche B, Duflo F, Tournadre JP, Debon R, Chassard D Influence of sepsis on sevoflurane minimum alveolar concentration in a porcine model. *Br J Anaesth* 2001; **86**: 832–6

23 Gill R, McKinnon T, Cunningham D, Sibbald WJ. Sepsis reduces isoflurane MAC in a normotensive animal model of sepsis. *Can J Anaesth* 1995; **42**; 631–5

24 Oguchi T, Kashimoto S, Yamaguchi T, Nakamura T, Kumazawa T Comparative effects of halothane, enflurane, isoflurane and sevoflurane on function and metabolism in the ischaemic working rat heart. *Br J Anaesth* 1995, **74**. 569–75

25 Heindl B, Reichle FM, Zahler S, Conzen PF, Becker BF. Sevoflurane and isoflurane protect the reperfused guinea pig heart by reducing postischemic adhesion of polymorphonuclear neutrophils. *Anesthesiology* 1999, **91**: 521–30

26 Kharasch ED, Karol MD, Lanni C, Sawchuk R. Clinical sevoflurane metabolism and disposition I Sevoflurane and metabolite pharmacokinetics. *Anesthesiology* 1995, **82**. 1369–78

27 Fink MP, Heard SO. Laboratory models of sepsis and septic shock. *J Surg Res* 1990; **49** 186–96

28 Sunnergren KP, Rovetto MJ. Myocyte and endothelial injury with ischemia reperfusion in isolated rat hearts. *Am J Physiol* 1987; **252**: H1211–7

29 Greenfield RA, Swain JL. Disruption of myofibrillar energy use. dual mechanisms that may contribute to postischemic dysfunction in stunned myocardium. *Circ Res* 1987, **60**. 283–9

30 Hotchkiss RS, Song S-K, Neil JJ, *et al*. Sepsis does not impair tricardboxylic acid cycle in the heart. *Am J Physiol* 1991; **260**: C50–7

31 Sargent CA, Dzwonczyk S, Sleph P, Wilde M, Grover GJ Pyruvate increases threshold for preconditioning in globally ischemic rat hearts. *Am J Physiol* 1994; **267**: H1403–9

British Journal of Anaesthesia 89 (6) 904–16 (2002)

BJA

REVIEW ARTICLE

Parkinson's disease and anaesthesia

G. Nicholson[1]*, A. C. Pereira[2] and G. M. Hall[1]

[1]Department of Anaesthesia and Intensive Care Medicine, St George's Hospital Medical School, Cranmer Terrace, London SW17 0RE, UK. [2]Department of Neurology, Charing Cross Hospital, Fulham Palace Road, London W6 8RF, UK

*Corresponding author. E-mail: gnichols@sghms.ac.uk

Parkinson's disease is an increasingly common disease of elderly patients who present a particular anaesthetic challenge. This review explores the epidemiology, aetiology, pathogenesis, and pathophysiology of the condition, particularly the possible role of genetic factors. The clinical features are described in detail and recent advances in medical management are highlighted. Controversies surrounding the use of the newer drugs and possible advances in neurosurgical interventions are discussed. Particular anaesthetic problems in patients with Parkinson's disease are respiratory, cardiovascular, and neurological. Potential drug interactions are described and recommendations are made about suitable anaesthetic techniques.

Br J Anaesth 2002; **89**: 904–16

Keywords: anaesthesia; complications, Parkinson's disease

> Involuntary tremulous motion, with lessened muscular power, in parts not in actions and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses being uninjured.
>
> James Parkinson, 1817.[92]

Parkinson's disease has been known since biblical times, but it was only in the nineteenth century that the syndrome was formally described by James Parkinson and termed 'the shaking palsy'.[92] In 1879, Charcot noted additional features including autonomic dysfunction.[15] The association between the substantia nigra and Parkinson's disease was discovered in 1893, but it was only in the latter half of the twentieth century that the neuropathological and neurochemical characteristics of the disease were elucidated and logical treatment strategies devised.[6 10 19 105]

Although the aetiology of Parkinson's disease is unknown, age has been identified as the most consistent risk factor; Parkinson's disease affects approximately 3% of the population over 66 yr of age.[76] Parkinson's disease is an important cause of perioperative morbidity and, with an increasingly elderly population, it will be encountered with greater frequency in surgical patients. Drugs used in anaesthesia may interact with anti-parkinsonian medication and there is controversy about the optimal anaesthetic management of patients with Parkinson's disease.

Epidemiology

Parkinson's disease occurs world wide, affecting all ethnic groups, with a very slight male preponderance.[139] The prevalence increases exponentially between 65 and 90 yr; approximately 0.3% of the general population and 3% of people over 65 yr have it.[76] The EUROPARKINSON study found an overall prevalence of 2.3% for parkinsonism and 1.6% for Parkinson's disease in a survey of 14 636 participants aged over 65 yr in five European countries.[109] As many as 24% of the subjects with Parkinson's disease were newly diagnosed at the time of the study. This highlights the difficulty of diagnosis and emphasizes that many elderly hospital patients may have undiagnosed Parkinson's disease. However, a recent study of more than 120 000 patients in London general practices suggested the incidence was considerably less.[114] Five to ten per cent of patients have symptoms before the age of 40 yr (so-called young-onset Parkinson's disease). The lowest reported incidence is among Asians and African blacks and the highest is amongst whites. The disease was first formally described during the Industrial Revolution,

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

suggesting that exogenous toxins may have a causative role, but descriptions of conditions resembling Parkinson's disease are found in literature dating back thousands of years BC.

Aetiology

The syndrome of *parkinsonism* (clinical conditions which resemble idiopathic Parkinson's disease) may have a number of different causes such as arteriosclerosis, diffuse central nervous system degenerative disease, repeated head trauma, tumour, metabolic defects such as Wilson's disease, heavy metal, or carbon monoxide poisoning. Drug-induced parkinsonism results from dopamine receptor block by drugs such as phenothiazines, butyrophenones, and metoclopramide. The observation of parkinsonian symptoms in heroin addicts who accidentally used 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP), a pethidine analogue, has led to the development of a useful animal model for the syndrome.[59] An epidemic of encephalitis lethargica in the 1920s was responsible for an outbreak of early onset parkinsonism with associated severe rigidity and respiratory complications.

Although the aetiology of Parkinson's disease is unknown, it has long been hypothesized that neurodegeneration is induced by genetic, environmental, or infectious disorders. Age is the single most consistent risk factor and it has been estimated that there is a cumulative lifetime risk of one in 40 for developing Parkinson's disease.[100] Loss of pigmented cells in the substantia nigra is the most consistent finding in Parkinson's disease and normally the quantity of nigral cells diminishes from 425 000 to 200 000 at 80 yr. In Parkinson's disease, the substantia nigra shows marked depletion of cells (<100 000) with replacement gliosis. In addition, tyrosine β-hydroxylase, the rate-limiting step in dopamine synthesis, also diminishes. The remaining cells contain the highly characteristic eosinophilic Lewy bodies. However, the pattern of nigral cell loss in Parkinson's disease differs from that due to normal ageing. In Parkinson's disease, cell loss is predominantly from the ventrolateral tier of the substantia nigra, but this region is relatively spared in normal subjects.[23] Furthermore, if ageing is the primary mechanism that accounts for the time course of functional decline, it does not adequately explain the huge inter-individual variability in rates of clinical progression of the disease.[41 138]

After ageing, a family history is the strongest predictor of an increased risk of developing the disease, although the role of a common environment must also be considered.[116] Relatively high rates of concordance have been identified amongst monozygotic twins, when one twin had young-onset disease.[123] Most of the available evidence supports an autosomal dominant inheritance of the disease, but many patients do not show this pattern of inheritance. This may reflect the fact that the causative genes have low penetrance or that the disease is multifactorial. To date, the identification of genes involved in the dopaminergic system has proved disappointing. The discovery of two distinct mutations in the α-synuclein gene (SNCA) located on chromosome 4q appeared to be a major breakthrough.[55 98] Alpha-synuclein is a highly conserved, abundant 140 amino acid protein of unknown function that is expressed mainly in presynaptic nerve terminals in the brain.[33] It appears to be a major component of Lewy bodies, the hallmark intracytoplasmic eosinophilic inclusion bodies, and its occurrence in Parkinson's disease suggests that this disease also belongs to those conditions, such as Alzheimer's, attributable to toxic protein aggregation.[14] Mutations in α-synuclein were reported in a number of unrelated families with a strong family history of Parkinson's disease, but several studies have failed to locate this genetic defect in other families or in sporadic cases, suggesting that Parkinson's disease is only rarely caused by such defects.[55] Similarly, attempts to implicate the detoxifying enzymes, debrisoquine 4-hydroxylase (CYP2D6) or *N*-acetyltranferase 2, in the pathogenesis of Parkinson's disease have been inconclusive.[5 107]

Parkinson's disease was first described during the industrial revolution suggesting that environmental toxins may play a role in its pathogenesis. The discovery of MPTP-induced parkinsonism lends further weight to this theory.[59] A rural environment has been associated with an increased risk of developing Parkinson's disease, suggesting that agents such as herbicides or pesticides may have an aetiological role, although this is limited to approximately 10% of patients with Parkinson's disease.[115] Cigarette smoking has been shown consistently to reduce the risk of developing Parkinson's disease,[39 79] although this may be restricted to those with a relatively young age at onset of the disease.[127] This effect has been attributed to inhibition of monoamine oxidase type B by products of tobacco combustion. Evidence linking dietary factors to Parkinson's disease is inconclusive, although one study has shown a lower vitamin E intake in patients with Parkinson's disease compared with controls.[108]

Overall, most cases of Parkinson's disease are likely to result from a combination of genetic and environmental factors and these differ between individuals. Genetic mutations may predispose patients to develop Parkinson's disease if combined with other gene mutations or environmental factors.[71]

Pathogenesis

Parkinson's disease is characterized by the progressive death of selected, but heterogeneous, populations of neurones, including those dopaminergic neurones of the pars compacta of the substantia nigra. The precise mechanisms responsible for cell death are largely unknown and may be due to mitochondrial dysfunction, oxidative stress, the actions of excitotoxins with excess nitric oxide formation, deficient neurotrophic support, or immune mechanisms.[57]

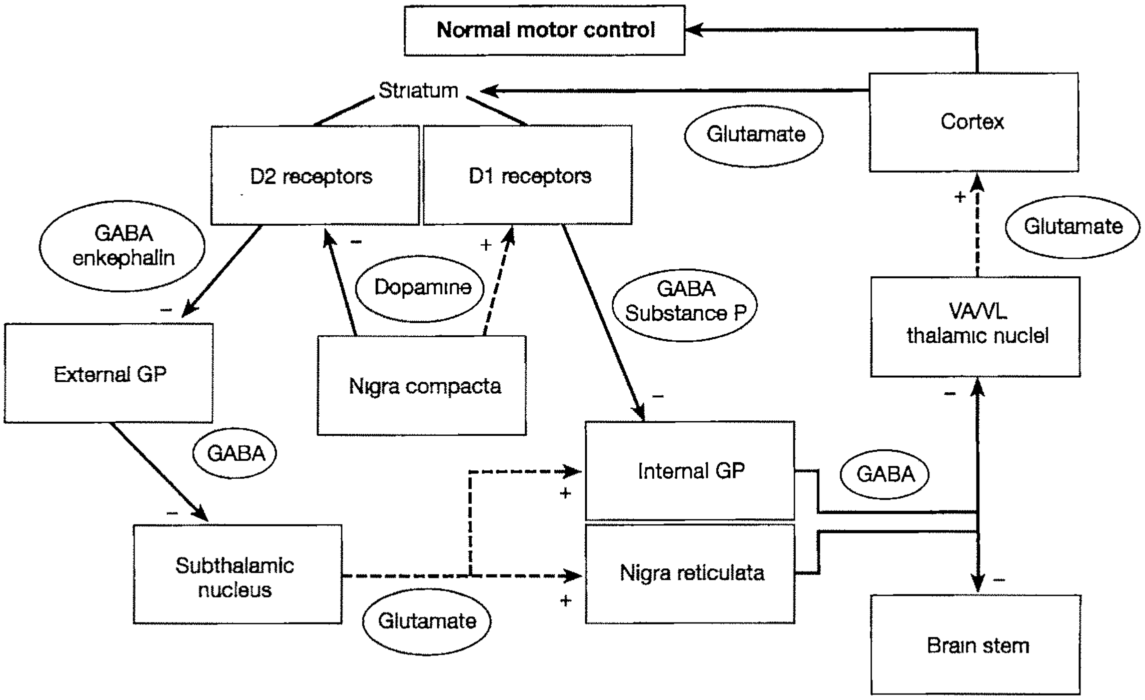


Fig 1 Normal motor control (reproduced with permission).[58]

Although still controversial, the final common pathway appears to be the induction of apoptosis in nigral dopaminergic neurones.[13,53]

Mitochondrial dysfunction and oxidative metabolism are major components of many current theories in Parkinson's disease. MPTP toxicity is due to inhibition of complex-1 of the mitochondrial electron transport chain, leading to lack of ATP and cell death. In Parkinson's disease, there is a 30–40% decrease in complex-1 activity in the substantia nigra pars compacta which may contribute to energy failure and hence predispose the pars compacta to toxic insults and increase its susceptibility to cell death.[68] Oxidative stress may be caused by an increase in the number of reactive species including hydrogen ions, superoxide, peroxyl radicals, nitric oxide, and hydroxyl radicals. These react with proteins, lipids, and nucleic acids altering their structure and function and causing cellular damage. Indeed, the metabolism of exogenous dopamine can also produce a number of toxic products and this knowledge prompted the concern that treatment of Parkinson's disease with L-DOPA may hasten the death of neurones in the substantia nigra pars compacta.[88] However, data about the potential toxicity of L-DOPA are conflicting and are not supported by clinical evidence.[103]

Other factors, which have been implicated in the pathogenesis of Parkinson's disease, include persistent activation of glutaminergic *N*-methyl-D-aspartate (NMDA) receptors resulting in increased intracellular concentrations of Ca^{2+}. This leads to the activation of proteases, endonucleases, phospholipases, and nitric oxide synthetase, which in turn generate reactive nitric oxide free radicals, release of iron from ferritin, and lipid peroxidation.[57] Neurotrophic factors are important in neuronal function and inadequate concentrations cause apoptotic cell death. Both glial-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF) are potent protective and regenerative agents, and animal studies have suggested that these may be deficient in Parkinson's disease leading to degeneration of dopaminergic cells.[60] Finally, immune factors may also contribute to neuronal cell loss. Increased concentrations of cytokines are found in the substantia nigra as the disease progresses, but it is unclear whether their role is primary or secondary.[124]

Pathophysiology

The basal ganglia refers to the areas of basal forebrain and midbrain known to be involved in the control of movement. They include the striatum, mainly comprising the caudate and putamen, the globus pallidus, the subthalamic nucleus, and the main pigmented component of the substantia nigra known as the pars compacta.[26] The clinically important motor circuit originates in the sensorimotor cortex and terminates in the supplementary motor area. The middle part of the loop divides into two pathways from striatum to thalamus. There is a one station direct pathway via the internal part of the pallidum and a three station indirect pathway via the external globus pallidus, the subthalamic nucleus and the internal globus pallidus. Hence, the internal globus pallidus is common to both pathways (Fig. 1).[58] The nigrostriatal pathway projects from the substantia nigra pars compacta to the striatum, where it makes two kinds of synapses on the projection neurones. Those upon direct pathway neurones are facilitatory via dopaminergic type 1

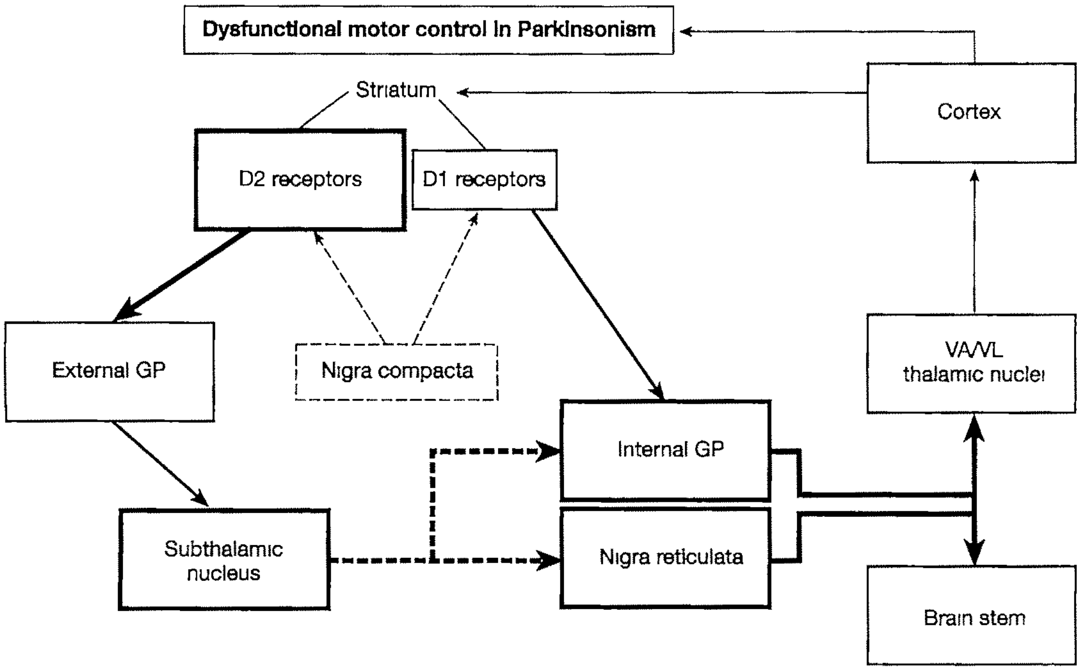


Fig 2 Dysfunctional control in Parkinsonism (reproduced with permission).[58]

(D1) receptors on the dendritic spines, and those upon indirect pathway neurones are inhibitory via D2 receptors. Cholinergic internuncial neurones are excitatory to projection neurones and are inhibited by dopamine. In Parkinson's disease, acetylcholine is present in normal amounts in the striatum. However, dopamine deficiency produces imbalance in the dopamine:acetylcholine ratio, thereby aggravating the symptoms of Parkinson's disease. A healthy substantia nigra is tonically active, favouring activity in the direct pathway. Facilitation of the direct pathway is necessary for the supplementary motor cortex to become active before and during movements.

Parkinson's disease is characterized by a loss of dopaminergic neurones in the substantia nigra of the basal ganglia (Fig. 2).[58] A decrease in dopamine production results in facilitation of the indirect pathway because of a lack of D1 facilitation of the direct pathway and of D2 inhibition of the indirect pathway. This dopamine deficient state is associated with increased activity of inhibitory nuclei in the basal ganglia (using the neurotransmitter γ-aminobutyric acid (GABA)), eventually leading to excessive inhibition, and effectively to a shutdown, of the thalamic and brainstem nuclei that receive the outflow from the basal ganglia. Excessive thalamic inhibition results in suppression of the cortical motor system with akinesia, rigidity and tremor, while inhibition of brainstem locomotor areas may contribute to abnormalities of posture and gait.

Diagnosis and clinical features

Parkinson's disease comprises a classical triad of resting tremor, muscle rigidity, and bradykinesia, with, in addition, loss of postural reflexes.[57] The clinical signs can remain surprisingly unilateral until the disease is well advanced.[61] Diagnostic difficulty arises because the clinical features may be subtle early in the disease and alternative diagnoses such as arthritis or depression may be considered until the disease progresses. One of the most prominent figures of the twentieth century, Adolf Hitler, suffered from idiopathic Parkinson's disease, which was largely unnoticed despite innumerable public appearances.[30] Furthermore, the classical clinical features are not exclusive to Parkinson's disease but may be exhibited in other, 'parkinsonian', syndromes. The primary process that yields the parkinsonian phenotype is depigmentation of the pars compacta in the substantia nigra and loss of dopaminergic neurones, which terminate in the basal ganglia. Therefore, conditions that affect the brainstem, or disrupt the dopaminergic pathway, or affect the basal ganglia, can present with parkinsonian features. Such conditions include cerebrovascular disease, neoplasia, repeated head trauma and metabolic defects such as Wilson's disease, heavy metal or carbon monoxide poisoning, and other neurodegenerative conditions.[57] Neurodegenerative parkinsonian syndromes may be associated with more extensive pathology in the brain and brainstem, and often have additional clinical features that may be collectively termed 'Parkinson-plus' syndromes. These conditions include progressive supranuclear palsy (PSP) with progressive restriction of vertical eye movements,[63 120] corticobasal degeneration with progressive limb stiffness, clumsiness, weakness, apraxia, and alien limb phenomenon,[110 122] multiple system atrophy[135] embracing olivopontocerebellar atrophy,[32] striatonigral degeneration[134] and Shy–Drager syndrome,[117] and diffuse

Lewy body disease characterized by early dementia and hallucinations.[65] There is no specific test to confirm Parkinson's disease, the diagnosis is made mainly on clinical grounds. Magnetic resonance imaging of the brain is usually normal in Parkinson's disease but may be useful in demonstrating cerebrovascular disease or widespread brainstem atrophy in other neurodegenerative disorders.[113] Autonomic dysfunction is common in parkinsonian disorders and is often present earlier and more severely in the 'Parkinson-plus' syndromes. Sphincter electromyography, reflecting degeneration of Onuf's nucleus, has been shown to be a useful test to distinguish Parkinson's disease from multiple system atrophy or PSP.[130]

In autopsy studies, the final diagnosis of Parkinson's disease was incorrect in over 20% of cases.[42 102] However, a more recent study reported that 8% of untreated patients who had been diagnosed early with Parkinson's disease had a different diagnosis after 7 yr follow-up.[45] The features that are particularly characteristic of idiopathic Parkinson's disease are asymmetry of symptoms (especially tremor) and a good response to L-DOPA;[57] over 90% of patients have a good response to L-DOPA early in the disease. L-DOPA is usually so effective in ameliorating the symptoms of Parkinson's disease that a poor response demands consideration of alternative diagnoses. L-DOPA is the most effective treatment for Parkinson's disease and patients may have very little disability for the first few years of the disease; falls are also relatively infrequent during this phase. However, as Parkinson's disease progresses, other features appear and patients may complain of fluctuations in motor ability, cognitive impairment and depression.[46 119] The later clinical features may reflect progression of the underlying neurodegenerative process beyond the nigrostriatal pathway to affect other brainstem, thalamic, or basal ganglia nuclei or complications of drug treatment, or both.[44] Motor fluctuations in their simplest form are usually related to drug timing. Patients may notice that the effect of L-DOPA wears off about an hour before the next expected dose. The patient may change from a motor state characterized by fairly normal ability to move (termed the 'on' state) to one dominated by bradykinesia or akinesia, termed the 'off' state. The 'off' state does not reflect a return to untreated parkinsonism but probably a rebound worsening of the motor condition.[101] In addition, abnormal movements (termed 'dyskinesias') may occur in either state. 'Off' period dyskinesias tend to be fixed and dystonic, whereas 'on' dyskinesias are thought to be related to peak levels of L-DOPA and are very mobile and choreiform. Occasionally, dyskinesias appear transiently after a dose of L-DOPA has been taken. Therefore, it is important to obtain a detailed history of dyskinesias related to the drug regimen to identify when during the L-DOPA cycle these events occur and whether they are related to wearing off, early or peak dose effects.

The tremor of Parkinson's disease is seen at rest, oscillates at about 4–6 Hz, has a characteristic 'pill rolling' quality, and ceases at the onset of movement.[24] The tremor becomes less marked with movement (unlike cerebellar tremors), but may be postural (brought out for example by holding a cup and saucer) like essential tremor.[73] However, essential tremor may be differentiated as it is autosomal dominant, often improved by alcohol and not associated with other parkinsonian features.[43 64] Parkinsonian tremor can be brought out by relaxing the patient's arm and asking them to count back from 100, subtracting seven each time. Testing finger-nose (or heel-shin) co-ordination emphasizes that the tremor is present mainly at rest. Rigidity often accompanies the tremor, giving it a 'cogwheeling' feel.[24 81] The best movements to test are flexion-extension at the elbow and wrist. Bradykinesia is a paucity of movement. The movements appear slow and there is a reduction in the amplitude of the finger excursions.[1] In addition to slowness of finger movements, handwriting is affected with micrographia an easily elicitable feature.[74] Facial expression may be affected giving rise to a characteristic, expressionless face. Parkinsonian patients may also demonstrate a variety of primitive reflexes including the glabellar tap sign.[131]

Clinical examination must include an assessment of posture and gait. The patient may have a slightly flexed posture. If the patient is asked to stand with their eyes shut and the examiner perturbs their equilibrium by a gentle push, either backwards or forwards (ensuring that the patient does not fall and hurt themselves), the patient may take several steps either backwards (retropulsion) or forwards (propulsion) before regaining their balance. This is because the postural reflexes are abnormal in Parkinson's disease.[11 125] About 80% of patients with Parkinson's disease experience gait hypokinesia at some stage of the disease.[80] In addition, gait initiation failure and freezing are common. If initiation of gait is impaired, the patient may lean forward to start moving. The gait comprises small steps, which may become more and more rapid (festination) and there may be reduced arm swing. Lack of arm swing on the same side as the tremor is very characteristic. Later in the disease, freezing of gait may become a major problem.[31 73] Patients often have difficulty turning and will turn taking many small shuffling steps on the spot.[80]

Examination of eye movements is very helpful in differentiating idiopathic Parkinson's disease from other parkinsonian conditions. Parkinson's disease patients may show slowness of initiation of voluntary saccades and jerkiness of pursuit movements.[12 47] However, markedly increased latency of voluntary saccades, or restriction and slowing of vertical eye movements with limitation of voluntary up and down gaze, suggests an alternative cause for parkinsonism such as corticobasal degeneration or PSP.[128]

Dysautonomia is often a feature of Parkinson's disease and other parkinsonian syndromes.[16] Patients with Parkinson's disease may suffer from orthostatic hypotension, urinary dysfunction and sleep disorders. Therefore, clinical assessment should include an assessment of these problems with measurement of arterial pressure lying, and standing, as there may be marked postural fluctuations.

Treatment of Parkinson's disease

Drug therapy

The aim of treatment of Parkinson's disease is to enable the patient to pursue a normal active lifestyle. The mainstay of treatment is drug therapy using L-DOPA or dopamine receptor agonists. The crucial factor is to educate the patient about the disease and how the drugs are likely to affect them. With guidance, patients can usually adapt a regimen to suit their particular lifestyle. The result may be that they take drugs at apparently peculiar times. A common scenario is that a patient's finely tuned drug regimen is thrown into disarray on admission to hospital when the drug timings are forced into the available boxes on the drug card. It is very important to record the exact times when a patient's drugs are due, and to try to reproduce these as far as practicable in hospital.

L-DOPA and dopamine agonists

The main deficit in Parkinson's disease is lack of availability of dopamine in the basal ganglia, so the logical treatment is to replace this with exogenous dopamine or stimulate the same receptors as endogenous dopamine. It is widely considered that the best treatment for Parkinson's disease is L-DOPA, a prodrug, which is converted to dopamine in the brain.[44 96] L-DOPA is administered in combination with a peripheral DOPA decarboxylase inhibitor to minimize peripheral dopamine side-effects. The alternative approach is to use dopamine agonists. Although these drugs may be very helpful in early Parkinson's disease, the effect is not sustained and patients often require combination therapy with L-DOPA as the disease progresses.[96] Dopamine agonists include bromocriptine,[52] ropinirole,[52] pergolide,[7] pramipexole,[8 77] and cabergoline.[111] Each agonist is effective in improving motor function in Parkinson's disease.[126] The main controversy in deciding whether to start treatment with L-DOPA or a dopamine agonist stems from the observation that initial use of L-DOPA may produce early dyskinesias. As L-DOPA has a short half-life (30–60 min), dopamine receptors are subject to phasic stimulation rather than the tonic stimulation that is thought to occur in normal basal ganglia function.[126] The mechanism of generation of dyskinesia is poorly understood but it is possible that the onset of dyskinesias is related to the short half-life of L-DOPA in the striatum.[44 126] A recent clinical trial confirmed that using a dopamine agonist before starting L-DOPA delayed the onset of dyskinesias,[104] yet L-DOPA remains the most effective agent for relieving symptoms and signs of Parkinson's disease.[118] The debate continues about whether to start treatment with a dopamine agonist or L-DOPA;[78 133] in younger patients, a dopamine agonist is tried first and then L-DOPA is added, if necessary.[118]

Apomorphine is a short-acting dopamine agonist that is administered subcutaneously, or sometimes sublingually or intranasally.[82] An important side-effect is nausea and vomiting, but with the concurrent use of domperidone it may be well tolerated.[82] It is particularly useful administered as an infusion to smooth out motor fluctuations or rescue patients from 'off' periods.[97] It is not widely available, as expertise supervising the use of infusion pumps is essential.

Monoamine oxide inhibitors

The type B monoamine oxidase inhibitor, selegiline is also used to treat Parkinson's disease and it prolongs the action of dopamine in the striatum. Selegiline improves the symptoms of Parkinson's disease but in addition there was a suggestion in the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) study,[93 136] that it may retard progression of the disease independent of its symptomatic effect and exert a neuroprotective effect.[50] The subsequent enthusiasm for selegiline was tempered in the UK by the publication of a report suggesting that, in combination with L-DOPA, it was associated with a 60% increased mortality compared with L-DOPA treatment alone.[62] However, the open labelled trial design, the large number of patients who withdrew from their original treatment assignment, the high mortality in both treatment groups, and the fact that no previous trial had demonstrated selegiline toxicity, made interpretation of the UK trial difficult.[90] There was no increase in mortality associated with selegiline in the DATATOP study.[94] A meta-analysis of trials of selegiline did not confirm an excess of deaths in selegiline-treated patients[91] and a recent case-controlled study reported that Parkinson's disease patients had a higher mortality compared with age-matched controls, but that mortality was not significantly increased by taking selegiline.[20] The role of selegiline in treating Parkinson's disease remains controversial.[82]

Alternative therapies

Within 5 yr of starting therapy for Parkinson's disease, half to two-thirds of patients will experience fluctuations in their motor symptoms.[70] With continued therapy, these fluctuations become more dependent on the plasma concentration of levodopa.[38] To ameliorate the fluctuations, the circulating dopamine concentration must be stabilized. This may be achieved by changing the dosing regimen or using a controlled release preparation of L-DOPA. Alternatively, a combination of L-DOPA and a dopamine agonist may be used. The agonist provides tonic dopamine receptor stimulation during the wearing off period. Another approach is to use catechol-*O*-methyl transferase (COMT) inhibitors, which inhibit the breakdown of dopamine in the periphery and increase its bioavailability.[38] Thus, COMT inhibitors may smooth out fluctuations in dopamine concentration which contribute to the wearing off, or on-off fluctuations, and improve the amount of 'on' time. The COMT inhibitors in common clinical use are tolcapone and entacapone. However, there is concern over tolcapone producing hepatotoxicity,[89] so entacapone is the preferred drug. If dyskinesias are very marked, amantadine may significantly diminish L-DOPA-induced dyskinesias.[66] Anticholinergic drugs such as benzhexol have limited efficacy and many side-effects, which limit their tolerability.[118] They may be useful in early disease to treat tremor (where bradykinesia is not a major problem).

Surgical treatment

An exciting development has been the advent of surgical treatment for Parkinson's disease. Surgical procedures comprise deep brain stimulation, ablative lesions and cell transplantation. Deep brain stimulation has the advantage that it is reversible and adjustable. In Parkinson's disease, the depletion of dopamine in the striatum leads to a series of changes in basal ganglia circuitry.[87] There is hyperactivity in the subthalamic nucleus, which is relayed as increased excitatory drive to the internal segment of the globus pallidus and thence as excessive inhibitory output to the thalamocortical motor projections (Fig. 2). This results in decreased cortical motor output manifested as bradykinesia. Chronic, deep-brain high-frequency stimulation mimics the effect of an ablative lesion. Pallidal stimulation has been reported to have a similar beneficial effect to pallidotomy. Subthalamic nucleus stimulation is the most promising surgical intervention for Parkinson's disease. Several studies have reported marked improvements in rigidity, tremor and bradykinesia. Bilateral stimulation is possible with further improvement in parkinsonian features. Unilateral thalamotomy, or thalamic stimulation, provide effective treatment for contralateral tremor in 75–85% of patients. The procedure is relatively safe if performed unilaterally. Bilateral lesions may produce dysarthria and dysphagia as well as cognitive problems. Pallidotomy involves lesions to the globus pallidus internum, and is effective in reducing contralateral dyskinesia and contralateral 'off' symptoms. Lastly, transplantation of fetal mesencephalic tissue into the striatum of Parkinson's disease patients has been reported to improve symptoms. Fetal grafts have been found to survive for several years and form synaptic connections. However, the technique is still experimental.[56 137]

Dopamine antagonist drugs, which may produce a parkinsonian syndrome or exacerbate the disease, must be avoided perioperatively. Metoclopramide is a surprisingly common cause of this problem. Treating postoperative confusion, or drug-induced psychosis, in Parkinson's disease may be difficult. The introduction of 'atypical' antipsychotic drugs (which have much reduced parkinsonian side-effects) has enabled the psychosis to be treated without exacerbating Parkinson's disease. Clozapine has been shown to be particularly effective in this respect[27 95] but causes fatal agranulocytosis in 1–2% of patients. Olazapine, risperidone and quetiapine are other antipsychotics which have been shown to be effective treatment for psychosis with fewer parkinsonian side-effects.[18 29] Another method of managing a Parkinson's disease patient with postoperative confusion is to use a benzodiazepine for sedation. Care must be taken to ensure that there is no respiratory depression, but this approach allows immediate control of the confusion while the cause (anaemia, infection, metabolic disturbance, etc.) is sought and treated.

Anaesthetic considerations

Patients with Parkinson's disease most commonly present for urology, ophthalmological, or orthopaedic procedures, and elderly surgical patients may have undiagnosed Parkinson's disease.[83] Anaesthetic management is also required for pallidotomy, thalamotomy, or neuroaugmentive procedures. Apart from a routine history, physical examination, and preoperative testing, patients with Parkinson's disease require additional assessment. Table 1 summarizes the recommendations for the patient with Parkinson's disease.

Respiratory system

Respiratory abnormalities have been noted in patients with Parkinson's disease since its initial description in 1817 and respiratory complications, particularly aspiration pneumonia, are the most common causes of death in these patients.[41] An obstructive ventilatory pattern has been observed in up to one-third of patients with Parkinson's disease,[85 86] but may also be due to co-existing chronic obstructive pulmonary disease.[86] However, there is evidence that abnormal control and function of the upper airway may be responsible for the airflow limitation observed in extrapyramidal disorders.[129] The intrinsic laryngeal muscles, and probably most of the other muscles surrounding the upper airway, are almost invariably involved in the involuntary movements characteristic of Parkinson's disease. Upper airway dysfunction is an important factor in the retained secretions, atelectasis, aspiration, and respiratory infection, which are frequently seen in patients with Parkinson's disease. Other potential complications include post-extubation laryngospasm and postoperative respiratory failure.[4 21] Sleep apnoea has been described in patients with post-encephalitic Parkinson's disease, but is now rarely seen.[48]

Autonomic nervous system

Autonomic manifestations in patients with Parkinson's disease are rarely specific. Changes in various systemic

Table 1 Recommended assessment of the patient with Parkinson's disease[72]

System	Assessment by history	Tests
Head and neck	Pharyngeal muscle dysfunction Dysphagia Sialorrhoea Blepharospasm	
Respiratory	Respiratory impairment from rigidity, bradykinesia or uncoordinated involuntary movement of the respiratory muscles	Chest x-ray Pulmonary function tests Arterial blood gas analysis
Cardiovascular	Orthostatic hypotension Cardiac arrhythmias Hypertension Hypovolaemia Autonomic dysfunction	ECG
Gastrointestinal	Weight loss Poor nutrition Susceptibility to reflux	Serum albumin/transferrin Skin test anergy
Urological	Difficulty in micturition	
Endocrine	Abnormal glucose metabolism (selegiline)	Blood glucose concentration
Musculoskeletal	Muscle rigidity	
CNS	Muscle rigidity Akinesia Tremor Confusion Depression Hallucinations Speech impairment	

functions such as gastrointestinal, are common in old age and Parkinson's disease, and data on their relative frequency and severity are not available. Moreover, they may also be iatrogenic as a result of the side-effects, of Parkinson's disease medication or other drugs. It is an unanswerable question whether an autonomic symptom is a manifestation of age, disease or therapy, or any combination of these factors. Patients with Parkinson's disease may complain of difficulty with salivation, micturition, and gastrointestinal function; some may also have defective cardiovascular control and temperature regulation. Seborrhoea, a classical feature of Parkinson's disease, is also an autonomic manifestation of the disease.[51]

Cardiovascular system

Cardiac arrhythmias and dependent oedema may occur, but the most disabling symptom is orthostatic hypotension.[36] Postural hypotension was observed in patients before the start of L-DOPA therapy and was not associated with any abnormality of the cardiovascular response to a Valsalva manoeuvre. However, in evaluating orthostatic hypotension in patients with Parkinson's disease, the role of medication must be considered. Several drugs for Parkinson's disease may cause or exacerbate hypotension including L-DOPA acting through a central mechanism similar to alpha-methyl DOPA, although before the use of decarboxylase inhibitors peripheral conversion to dopamine also contributed to its hypotensive effect. Direct-acting dopamine agonists, such as bromocriptine and lisuride, may precipitate hypotension by causing peripheral vasodilation. Finally, use of older antidepressants such as amitriptyline and other tricyclic antidepressants may cause orthostatic hypotension.

Gastrointestinal function

Disturbances of gastrointestinal function are probably the most common autonomic features in Parkinson's disease. In his original monograph, James Parkinson wrote 'The power of conveying food to the mouth is at length so much impeded that he is obliged to be fed by others. The bowels, which had been all along torpid, now, in most cases, demand stimulating medicines of very considerable power. . .'.[92] Sialorrhoea is a common late manifestation of the disease but is probably due to reduced automatic swallowing and hence the poverty of motor movement rather than autonomic dysfunction. The amount of saliva produced is normal and the symptom responds to L-DOPA administration. However, the use of antimuscarinic drugs increases the viscosity of saliva and further impairs swallowing. The pathogenesis of dysphagia and abnormalities of oesophageal function is unclear. However, the discovery of Lewy bodies in the oesophageal myenteric plexus of a patient who had achalasia, but no extra pyramidal symptoms, may provide some clues.[99] Constipation and mild weight loss are also common.

Anaesthesia in the patient with Parkinson's disease

General considerations

The usual drug regimen should be administered as close to the beginning of anaesthesia as possible. L-DOPA can only be administered enterally and its half-life is short (1–3 h). It is absorbed from the proximal small bowel and, therefore, cannot be given as a suppository. Patients may self-administer additional L-DOPA, so it is important to find out exactly how much they are taking.[106] Furthermore, it is essential to ensure that patients do not miss medication doses postoperatively. Patients should be able to take L-DOPA either with sips of water or by nasogastric tube. Another strategy is to use subcutaneous administration of apomorphine. However, this is very emetogenic and patients usually need to take domperidone for several days before an apomorphine challenge. Nevertheless, small doses of apomorphine with sufficient antiemetic cover may be helpful.

Regional anaesthesia has obvious advantages over general anaesthesia as it avoids the effects of general anaesthetics and neuromuscular blocking drugs, which may mask tremor. If sedation is required, diphenhydramine has been described as useful particularly for ophthalmic procedures.[121] Its central anticholinergic activity is advantageous for patients with Parkinson's disease in whom tremor can render surgery difficult. With regional anaesthesia, postoperative nausea and vomiting, which may prevent resumption of oral intake, is also avoided. If general anaesthesia is required, it is worth noting that L-DOPA can be administered intraoperatively via a nasogastric tube.[28] Emergence from anaesthesia, even in healthy patients, is often marked by the transient appearance of a variety of what are otherwise considered to be pathological neurological reflexes, including hyperreactive stretch reflexes, ankle clonus, the Babinski reflex, and decerebrate posturing.[112] Shivering is common after general anaesthesia and regional analgesia and, again, should be distinguished from parkinsonian symptoms. Rigidity after both high-dose[67] and lower-dose[17] fentanyl is also well described in normal patients. Patients with Parkinson's disease are more prone to postoperative confusion and hallucinations.[34]

Drugs that precipitate or exacerbate Parkinson's disease should be avoided, including phenothiazines, butyrophenones (including droperidol), and metoclopramide. The latter may cause drug-induced Parkinson's disease. This is treated simply by drug withdrawal, but an obvious pitfall may be the misdiagnosis of idiopathic Parkinson's disease and administration of L-DOPA.[3] Potential drug interactions must also be considered. Patients on MAOIs have long been a specific concern of anaesthetists, but with the widespread use of selegiline, a MAOI-B type inhibitor, the likelihood of having to anaesthetize a patient receiving a MAOI-A inhibitor is decreased. However, there are reports of agitation, muscle rigidity and hyperthermia in patients receiving meperidine and selegiline, so this combination should be avoided.[140] The use of potent non-steroidal anti-inflammatory agents has avoided the need for narcotic analgesics in patients on MAOIs undergoing relatively minor procedures.[25]

Inhalational anaesthetics

Inhalational anaesthetic agents have complex effects on brain dopamine concentrations, inhibiting synaptic reuptake of dopamine, thereby increasing its extracellular concentration[22] and affecting both spontaneous and depolarization-evoked dopamine release.[69] These changes occur at clinically relevant concentrations of anaesthetic agents. For patients taking L-DOPA, anaesthetic agents such as halothane, which sensitizes the heart to the action of catecholamines, should be avoided. The newer inhalational agents, isoflurane and sevoflurane, are less arrhythmogenic, but hypotension is still a concern due to hypovolaemia, norepinephrine depletion, autonomic dysfunction and the co-administration of other medication. Patients taking bromocriptine or pergolide are prone to excessive vasodilation further exacerbating hypotension. Of historical interest, chronic trichloroethylene exposure has been implicated in the development of parkinsonism.[37]

Intravenous induction agents

Previous case reports have described parkinsonian episodes in patients receiving thiopental,[21 83] and in animal studies thiopental decreased dopamine release from striatal synaptosomes.[69] The clinical significance of this is unclear and thiopental has not been directly implicated in exacerbating parkinsonian symptoms. Ketamine is theoretically contraindicated in Parkinson's disease because of an exaggerated sympathetic response, but it has been used in these patients without harm.[40] Recent interest has focused on the use of propofol in patients with Parkinson's disease, particularly those undergoing stereotactic pallidotomy or thalamotomy. Theoretically, propofol is an ideal agent to use while attaching the stereotactic frame, because of its rapid metabolism and emergence profile. Again, there is a paucity of evidence about its effects in patients with Parkinson's disease but case reports have described both dyskinetic effects,[54] and abolition of tremor,[2] in patients scheduled for stereotactic procedures leading to cancellation of surgery. As patients presenting for stereotactic surgery have their anti-parkinsonian medication stopped for 12–24 h preoperatively, so that their symptoms may be observed and then seen to be abolished, the second case report recommended that propofol is not used for these procedures because of its unpredictable effects.[2]

Table 2 Possible drug interactions in patients with Parkinson's disease

Drug	Comments
Induction agents	
Propofol	Avoid for stereotactic procedures[2, 54]
Etomidate	Probably safe
Thiopental	Probably safe
Analgesics	
Fentanyl	Possible muscle rigidity[17, 49, 67]
Meperidine	Avoid in patients on selegiline[140]
Morphine	Possible muscle rigidity[9]
Alfentanil	Possible dystonic reactions[75]
Volatile agents	
Isoflurane	Probably safe
Sevoflurane	Probably safe
Enflurane	Probably safe
Halothane	Possible arrhythmias
Neuromuscular blocking drugs	
Succinylcholine	Possible hyperkalaemia[35, 84]
Non-depolarizing agents	Probably safe

Neuromuscular blocking agents

There are no reported cases of non-depolarizing neuromuscular blocking drugs worsening the symptoms of Parkinson's disease. Succinylcholine has been reported to cause hyperkalaemia in a patient with Parkinson's disease,[35] although the case was complicated by other factors. A later case series looked at seven patients with Parkinson's disease, who received succinylcholine as part of their anaesthetic management and found no signs of succinylcholine-induced hyperkalaemia.[84]

Opioids

There are numerous reports of muscle rigidity following the use of fentanyl in normal patients, and those with an established diagnosis of Parkinson's disease.[49] Opioid-induced muscle rigidity responds to neuromuscular block and is postulated to result from presynaptic inhibition of dopamine release.[132] Morphine has, however, also been shown to be associated with a reduction of dyskinesia at very low doses and an increase in akinesia at higher doses in patients with Parkinson's disease.[9] Acute dystonia after alfentanil has also been described,[75] and the severe interaction between meperidine and selegiline has already been noted.[140]

It is clear that there is no simple anaesthetic regimen for patients with Parkinson's disease. Much of the evidence about the safety of various anaesthetic drugs or techniques is based on single case reports or small case series. The absence of randomized controlled trials evaluating various anaesthetic techniques or drugs means that advice can only be based on data that have obvious limitations. What is apparent from these reports is that most patients with Parkinson's disease are elderly with coexisting medical conditions as well as the complications of the disease and its treatment. Meticulous preoperative assessment, maintenance of drug therapy up to the time of anaesthesia and afterwards, avoiding known precipitating agents and intraoperative administration of L-DOPA if required, are key factors in the reduction of postoperative morbidity. These recommendations are summarized in Table 2.

References

1 Agostino R, Berardelli A, Curra A, Accornero N, Manfredi M. Clinical impairment of sequential finger movements in Parkinson's disease. *Mov Disord* 1998; **13**: 418–21

2 Anderson BJ, Marks PV, Futter ME. Propofol—contrasting effects in movement disorders. *Br J Neurosurg* 1994; **8**: 387–8

3 Avorn J, Gurwitz JH, Bohn RL, Mogun H, Monane M, Walker A. Increased incidence of levodopa therapy following metoclopramide use. *JAMA* 1995; **274**: 1780–2

4 Backus WW, Ward RR, Vitkun SA, Fitzgerald D, Askanazi J. Postextubation laryngospasm in an unanaesthetised patient with Parkinson's disease. *J Clin Anesth* 1991; **3**: 314–6

5 Bandmann O, Vaughan J, Holmans P, Marsden CD, Wood NW Association of slow acetylator genotype for *N*-acetyltransferase 2 with familial Parkinson's disease. *Lancet* 1997; **350**: 1136–9

6 Barbeau A. The pathogenesis of Parkinson's disease: a new hypothesis. *Can Med Assoc J* 1962; **87**: 802–7

7 Barone P, Bravi D, Bermejo-Pareja F, *et al.* Pergolide monotherapy in the treatment of early PD: a randomized, controlled study. Pergolide Monotherapy Study Group. *Neurology* 1999; **53**: 573–9

8 Bennett JP, Piercey MF. Pramipexole—a new dopamine agonist for the treatment of Parkinson's disease. *J Neurol Sci* 1999; **163**: 25–31

9 Berg D, Becker G, Reiners K. Reduction of dyskinesia and induction of akinesia induced by morphine in two parkinsonian patients with severe sciatica. *J Neural Transm* 1999; **106**: 725–8

10 Birkmayer W, Hornikewicz O. Der L-dioxyphenylalanin (L-DOPA) Effekt bei der Parkinson-akinase. *Wien Klin Wschr* 1961; **73**: 787–8

11 Bloem BR, Beckley DJ, Remler MP, Roos RA, van Dijk JG. Postural reflexes in Parkinson's disease during 'resist' and 'yield' tasks. *J Neurol Sci* 1995; **129**: 109–19

12 Briand KA, Strallow D, Hening W, Poizner H, Sereno AB. Control of voluntary and reflexive saccades in Parkinson's disease. *Exp Brain Res* 1999; **129**: 38–48

13 Burke RE. Programmed cell death and Parkinson's disease. *Mov Disord* 1998; **13**: 17–23

14 Burke RE. α-Synuclein and parkin: coming together of pieces in puzzle of Parkinson's disease. *Lancet* 2001; **358**: 1567–8

15 Charcot JM. Lecture V. On paralysis agitans. In: Sigerson G, ed. *Lectures on Diseases of the Nervous System*. Philadelphia: HC Lea, 1879

16 Chaudhuri KR. Autonomic dysfunction in movement disorders. *Curr Opin Neurol* 2001; **14**: 505–11

17 Comstock MK, Scamman FL, Carter JG, Moyers JR, Stevens WC. Rigidity and hypercarbia on fentanyl-oxygen induction. *Anesthesiology* 1979; **51**: S28

18 Conley RR, Mahmoud R. A randomized double-blind study of risperidone and olanzapine in the treatment of schizophrenia or schizoaffective disorder. *Am J Psychiat* 2001; **158**: 765–74

19 Cotzias GC, Van Woert MH, Schiffer LM. Aromatic amino acids and modification of parkinsonism. *N Engl J Med* 1967; **276**: 374–9

20 Donnan PT, Steinke DT, Stubbings C, Davey PG, MacDonald TM. Selegiline and mortality in subjects with Parkinson's disease: a longitudinal community study. *Neurology* 2000; **55**: 1785–9

21 Easdown LJ, Tessler MJ, Minuk J. Upper airway involvement in

Parkinson's disease resulting in postoperative respiratory failure. *Can J Anaesth* 1995; **42**: 344–7

22 El-Maghrabi EA, Eckenhoff RG. Inhibition of dopamine transport in rat brain synaptosomes by volatile anesthetics. *Anesthesiology* 1993; **78**: 750–6

23 Fearnley JM, Lees AJ. Ageing and Parkinson's disease: substantia nigra regional selectivity. *Brain* 1991; **114**: 2283–301

24 Findley LJ, Gresty MA, Halmagyi GM. Tremor, the cogwheel phenomenon and clonus in Parkinson's disease. *J Neurol Neurosurg Psych* 1981; **44**: 534–46

25 Fischer SP, Mantin R, Brock-Utne JG. Ketorolac and propofol anesthesia in a patient taking chronic monoamine oxidase inhibitors. *J Clin Anesth* 1996; **8**: 245–7

26 Fitzgerald MJT. Basal ganglia. In: Fitzgerald MJT, ed. *Neuroanatomy Basic and Clinical*, 3rd Edn. London: WB Saunders Company Ltd, 1996: 247–55

27 The French Clozapine Parkinson Study Group Clozapine in drug-induced psychosis in Parkinson's disease. The French Clozapine Parkinson Study Group. *Lancet* 1999; **353**: 2041–2

28 Furuya R, Hirai A, Andoh T, Kudoh I, Okumura F. Successful perioperative management of a patient with Parkinson's disease by enteral levodopa administration under propofol anaesthesia. *Anesthesiology* 1998; **89**: 261–3

29 Geddes J, Freemantle N, Harrison P, Bebbington P. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. *Br Med J* 2000; **321**: 1371–6

30 Gerstenbrand F, Karamat E. Adolf Hitler's Parkinson disease and an attempt to analyse his personality structure. *Eur J Neurol* 1999; **6**: 121–7

31 Giladi N, McDermott MP, Fahn S, *et al.* and the Parkinson Study Group. Freezing of gait in PD: prospective assessment in the DATATOP cohort. *Neurology* 2001; **56**: 1712–21

32 Gilman S, Little R, Johanns J, *et al.* Evolution of sporadic olivopontocerebellar atrophy into multiple system atrophy. *Neurology* 2000; **55**: 527–32

33 Goedert M. Familial Parkinson's disease: the awakening of α-synuclein. *Nature* 1997; **388**: 232–3

34 Golden WE, Lavender RC, Metzer WS. Acute postoperative confusion and hallucinations in Parkinson's disease *Ann Intern Med* 1989; **111**: 218–22

35 Gravlee GP. Succinylcholine-induced hyperkalaemia in a patient with Parkinson's disease. *Anesth Analg* 1980; **59**: 444–6

36 Gross M, Bannister R, Godwin-Austin R. Orthostatic hypotension in Parkinson's disease. *Lancet* 1972; **1**: 174–6

37 Guehl D, Bezard E, Dovero S, Boraud T, Bioulac B, Gross C Trichlorethylene and parkinsonism: a human and experimental observation. *Eur J Neurol* 1999; **6**: 609–11

38 Hanson MR, Galvez-Jimenez N. Catechol-O-methyltransferase inhibitors in the management of Parkinson's disease. *Sem Neurol* 2001; **21**: 15–22

39 Hellenbrand W, Seidler A, Robra BP, *et al.* Smoking and Parkinson's disease: a case control study in Germany. *Int J Epidemiol* 1997; **26**: 328–39

40 Hetherington A, Rosenblatt RM. Ketamine and paralysis agitans. *Anesthesiology* 1980; **52**: 527

41 Hoehn MM, Yahr MD. Parkinsonism. onset, progression and mortality. *Neurology* 1967; **17**: 427–42

42 Hughes AJ, Daniel SE, Blankson S, Lees AJ. A clinicopathologic study of 100 cases of Parkinson's disease. *Arch Neurol* 1993; **50**: 140–8

43 Jankovic J. Essential tremor clinical characteristics. *Neurology* 2000; **54**: S21–5

44 Jankovic J. Complications and limitations of drug therapy for Parkinson's disease. *Neurology* 2000; **55**: S2–6

45 Jankovic J, Rajput AH, McDermott MP, Perl DP. The evolution of diagnosis in early Parkinson disease Parkinson Study Group. *Arch Neurol* 2000; **57**: 369–72

46 Jankovic J, Kapadia AS. Functional decline in Parkinson disease. *Arch Neurol* 2001; **58**: 1611–15

47 Kennard C, Lueck CJ Oculomotor abnormalities in diseases of the basal ganglia. *Revue Neurologique* 1989; **145**: 587–95

48 Kim R. The chronic residual respiratory disorder in post-encephalitic parkinsonism. *J Neurol Neurosurg Psych* 1968; **31**: 393–8

49 Klausner JM, Caspi J, Lelcuk S, *et al.* Delayed muscle rigidity and respiratory depression following fentanyl anesthesia. *Arch Surg* 1988; **123**: 66–7

50 Koller WC. Neuroprotection for Parkinson's disease. *Ann Neurol* 1998; **44**: S155–9

51 Korczyn AD. Autonomic nervous system disorders in Parkinson's disease. In: Streifler MB, Korczyn AD, Melamed E, Youdim MBH, eds. *Advances in Neurology, Vol 53: Parkinson's disease: Anatomy, Pathology and Therapy*. New York: Raver Press, 1990: 463–8

52 Korczyn AD, Brunt ER, Larsen JP, Nagy Z, Poewe WH, Ruggieri, S. A 3-year randomized trial of ropinirole and bromocriptine in early Parkinson's disease. The 053 Study Group. *Neurology* 1999; **53**: 364–70

53 Kosel S, Egensperger R, von Eitzen U, Mehraein P, Graeber MB. On the question of apoptosis in the parkinsonian substantia nigra. *Acta Neuropath (Berl)* 1997; **93**: 105–8

54 Krauss JK, Akeyson EW, Giam P, Jankovic J. Propofol-induced dyskinesias in Parkinson's disease. *Anesth Analg* 1996; **83**: 420–2

55 Kruger R, Kuhn W, Müller T, *et al.* Ala30Pro mutation in the gene encoding α-synuclein in Parkinson's disease. *Nat Genet* 1998; **18**: 106–8

56 Lang AE. Surgery for Parkinson disease: A critical evaluation of the state of the art. *Arch Neurol* 2000; **57**: 1118–25

57 Lang AE, Lozano AM. Parkinson's disease: first of two parts. *N Engl J Med* 1998; **339**: 1044–53

58 Lang AE, Lozano AM. Parkinson's disease: second of two parts. *N Engl J Med* 1998; **339**. 1130–43

59 Langston JW, Ballard P, Tetrud JW, Irwin I. Chronic parkinsonism in humans due to a product of meperidine analogue synthesis. *Science* 1983; **219**: 979–80

60 Lapchak PA, Miller PJ, Jiao S, Araujo DM, Hilt D, Collins F. Biology of glial cell line-derived neurotrophic factor (GDNF): implications for the use of GDNF to treat Parkinson's disease. *Neurodegeneration* 1996; **5**: 197–205

61 Lee CS, Schulzer M, Mak E, Hammerstad JP, Calne S, Calne DB. Patterns of asymmetry do not change over the course of idiopathic parkinsonism: implications for pathogenesis. *Neurology* 1995; **45**: 435–9

62 Lees AJ. Comparison of therapeutic effects and mortality data of levodopa and levodopa combined with selegiline in patients with early, mild Parkinson's disease. Parkinson's Disease Research Group of the United Kingdom. *Br Med J* 1995; **311**: 1602–7

63 Litvan I. Diagnosis and management of progressive supranuclear palsy. *Sem Neurol* 2001; **21**: 41–8

64 Louis ED. Clinical practice. Essential tremor. *N Engl J Med* 2001; **345**: 887–91

65 Louis ED, Goldman JE, Powers JM, Fahn S. Parkinsonian features of eight pathologically diagnosed cases of diffuse Lewy body disease. *Mov Disord* 1995; **10**: 188–94

66 Luginger E, Wenning GK, Bosch S, Poewe, W. Beneficial effects of amantadine on L-dopa-induced dyskinesias in Parkinson's disease. *Mov Disord* 2000; **15**: 873–8

67 Lunn JK, Stanley TH, Eisele J, Webster L, Woodward A. High dose fentanyl for cardiac surgery. *Anesth Analg* 1979; **58**: 390–5

68 Mann VM, Cooper JM, Krige D, Daniel SE, Schapira AH, Marsden CD. Brain, skeletal muscle and platelet homogenate mitochondrial function in Parkinson's disease *Brain* 1992; **115**: 33–42

69 Mantz J, Varlet C, Lecharny JB, Henzel D, Lenot P, Desmonts JM. Effects of volatile anaesthetics, thiopental and ketamine on spontaneous and depolarization-evoked dopamine release from striatal synaptosomes in the rat. *Anesthesiology* 1994; **80**: 352–63

70 Marsden CD, Parkes D. Success and problems of long-term levodopa therpay in Parkinson's disease. *Lancet* 1977; **1**: 345–9

71 Marsden CD, Olanow CW. The causes of Parkinson's disease are being unravelled and rational neuroprotective therapy is close to reality. *Ann Neurol* 1998; **44**: S189–96

72 Mason LJ, Cojocaru TT, Cole DJ. Surgical intervention and anaesthetic management of the patient with Parkinson's disease. *Int Anesth Clin* 1996; **34**: 133–50

73 McAuley JH, Marsden CD. Physiological and pathological tremors and rhythmic central motor control. *Brain* 2000; **123**: 1545–67

74 McLennan JE, Nakano K, Tyler HR, Schwab RS. Micrographia in Parkinson's disease. *J Neurol Sci* 1972; **15**: 141–52

75 Mets B. Acute dystonia after alfentanil in untreated Parkinson's disease. *Anesth Analg* 1991; **72**: 557–8

76 Moghal S, Rajput AH, D'Arcy C, Rajput R. Prevalence of movement disorders in elderly community residents. *Neuroepidemiology* 1994; **13**: 175–8

77 Moller JC, Oertel WH. Pramipexole in the treatment of advanced Parkinson's disease. *Eur J Neurol* 2000, **7** (Suppl 1): 21–5

78 Montastruc JL, Rascol O, Senard JM. Treatment of Parkinson's disease should begin with a dopamine agonist. *Mov Disord* 1999; **14**: 725–30

79 Morens DM, Grandinetti A, Reed D, White LR, Ross GW. Cigarette smoking and protection from Parkinson's disease: false association or etiological clue? *Neurology* 1995; **45**: 1041–51

80 Morris ME, Huxham FE, McGinley J, Iansek R. Gait disorders and gait rehabilitation in Parkinson's disease. *Adv Neurology* 2001; **87**: 347–61

81 Moyer H. A new diagnostic sign in paralysis agitans, the cogwheel resistance of the extremities. *JAMA* 1911; **57**: 2125

82 Munchau A, Bhatia KP Pharmacological treatment of Parkinson's disease. *Postgrad Med J* 2000; **76**: 602–10

83 Muravchick S, Smith DS. Parkinsonian symptoms during emergence from general anaesthesia. *Anesthesiology* 1995; **82**. 305–7

84 Muzzi DA, Black S, Cucchiara RF. The lack of effect of succinylcholine on serum potassium in patients with Parkinson's disease *Anesthesiology* 1989, **71**: 322

85 Neu HC, Connolly JJ, Schwertley FW, Ladwig HA, Brody AW. Obstructive respiratory dysfunction in parkinsonian patients. *Am Rev Respir Dis* 1967; **95**: 33–47

86 Obenour WH, Stevens PM, Cohen AA, McCutchen JJ. The causes of abnormal pulmonary function in Parkinson's disease *Am Rev Respir Dis* 1972; **105**: 382–7

87 Obeso JA, Rodriguez-Oroz MC, Rodriguez M, *et al.* Pathophysiologic basis of surgery for Parkinson's disease. *Neurology* 2000; **55**: S7–S12

88 Olanow CW. A rationale for using dopamine agonists as a primary symptomatic therapy in Parkinson's disease. In: Olanow CW, Obeso JA, eds. *Dopamine Agonists in Early Parkinson's Disease*. Royal Tunbridge Wells: Wells Medical, 1997: 37–48

89 Olanow CW. Tolcapone and hepatotoxic effects. Tasmar Advisory Panel. *Arch Neurol* 2000; **57**: 263–7

90 Olanow CW, Fahn S, Langston JW, Godbold J. Selegiline and mortality in Parkinson's disease. *Ann Neurol* 1996; **40** 841–5

91 Olanow CW, Myllyla VV, Sotaniemi KA, *et al.* Effect of selegiline on mortality in patients with Parkinson's disease: a meta-analysis. *Neurology* 1998; **51**: 825–30

92 Parkinson J. *An Essay on the Shaking Palsy*. London. Sherwood, Neely, and Jones, 1817

93 The Parkinson Study Group. Effect of deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med* 1989; **321**. 1364–71

94 The Parkinson Study Group. Mortality in DATATOP: a multicenter trial in early Parkinson's disease. *Ann Neurol* 1998; **43**: 318–25

95 The Parkinson Study Group. Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. *N Engl J Med* 1999; **340**: 757–63

96 Poewe W. Should treatment of Parkinson's disease be started with a dopamine agonist? *Neurology* 1998; **51**. S21–S24

97 Poewe W, Wenning GK. Apomorphine: an underutilized therapy for Parkinson's disease *Mov Disord* 2000; **15**: 789–94

98 Polymeropoulos MH, Lavedan C, Leroy E, *et al.* Mutation in the α-synuclein gene identified in families with Parkinson's disease. *Science* 1997; **276**: 2045–7

99 Qualman SJ, Haupt HM, Yang P, Hamilton SR Esophageal Lewy bodies associated with ganglion cell loss in achalasia. Similarity to Parkinson's disease. *Gastroenterology* 1984, **87**. 848–56

100 Quinn N. Parkinsonism—recognition and differential diagnosis *Br Med J* 1995; **310**. 145–50

101 Quinn NP. Classification of fluctuations in patients with Parkinson's disease. *Neurology* 1998; **51**: S25–S29

102 Rajput AH, Rozdilsky B, Rajput A. Accuracy of clinical diagnosis in parkinsonism—a prospective study. *Can J Neurol Sci* 1991, **18**: 275–8

103 Rajput AH, Fenton ME, Birdi S, Macaulay R. Is levodopa toxic to human substantia nigra? *Mov Disord* 1997; **12**. 634–8

104 Rascol O, Brooks DJ, Korczyn AD, DeDeyn PP, Clarke CE, Lang AE. A five year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. 056 Study Group. *N Engl J Med* 2000, **342**: 1484–91

105 Redfern RM History of stereotactic surgery for Parkinson's disease *Br J Neurosurg* 1989; **3**. 271–304

106 Reed AP, Han DG. Intraoperative exacerbation of Parkinson's disease. *Anesth Analg* 1992; **75**. 850–3

107 Riedl AG, Watts PM, Jenner P, Marsden CD. P450 enzymes and Parkinson's disease: the story so far. *Mov Disord* 1998; **13**: 212–20

108 deRijk MC, Breteler MMB, den Breeijen JH, *et al* Dietary antioxidants and Parkinson's disease: the Rotterdam study. *Arch Neurol* 1997; **54**: 762–5

109 deRijk MC, Tzourio C, Breteler MMB, *et al* Prevalence of parkinsonism and Parkinson's disease in Europe: the EUROPARKINSON collaborative study. *J Neurol Neurosurg Psych* 1997, **62**: 10–15

110 Rinne JO, Lee MS, Thompson PD, Marsden CD Corticobasal degeneration. A clinical study of 36 cases. *Brain* 1994, **117** 1183–96

111 Rinne UK, Bracco F, Chouza C, *et al.* Early treatment of Parkinson's disease with cabergoline delays the onset of motor complications. Results of a double-blind levodopa controlled trial. The PKDS009 Study Group. *Drugs* 1998; **55** (Suppl 1): 23–30

112 Rosenberg H, Clofine R, Bialik O. Neurologic changes during awakening from anaesthesia. *Anesthesiology* 1981; **54**: 125–30

113 Schrag A, Kingsley D, Phatouros C, *et al.* Clinical usefulness of magnetic resonance imaging in multiple system atrophy. *J Neurol Neurosurg Psych* 1998; **65**: 65–71

114 Schrag A, Ben-Shlomo Y, Quinn NP. Cross sectional prevalence survey of idiopathic Parkinson's disease and parkinsonism in London. *Br Med J* 2000; **321**: 21–2

115 Semchuk KM, Love EJ, Lee RG. Parkinson's disease and exposure to agricultural work and pesticide chemicals. *Neurology* 1992; **42**: 1328–35

116 Semchuk KM, Love EJ, Lee RG. Parkinson's disease: a test of the multifactorial etiologic hypothesis. *Neurology* 1993; **43**: 1173–80

117 Shy GM, Drager GA. A neurologic syndrome associated with orthostatic hypotension. *Arch Neurol* 1960; **2**: 511–27

118 Silver DE, Ruggieri S. Initiating therapy for Parkinson's disease *Neurology* 1998; **50**: S18–S22

119 Slaughter JR, Slaughter KA, Nichols D, Holmes SE, Martens MP. Prevalence, clinical manifestations, aetiology and treatment of depression in Parkinson's disease. *J Neuropsych Clin Neurosci* 2001; **13**: 187–96

120 Steele JC, Richardson JC, Olszewski J. Progressive supranuclear palsy. A heterogeneous degeneration involving the brain stem, basal ganglia and cerebellum with vertical gaze and pseudobulbar palsy, nuchal dystonia and rigidity. *Arch Neurol* 1964; **10**: 337–59

121 Stone DJ, Difazio CA. Sedation for patients with Parkinson's disease undergoing ophthalmic surgery. *Anesthesiology* 1988; **68**: 821

122 Stover NP, Watts RL. Corticobasal degeneration. *Sem Neurol* 2001; **21**: 49–58

123 Tanner CM, Ottman R, Goldman SM, *et al.* Parkinson's Disease in twins; an etiological study. *JAMA* 1999; **281**: 341–6

124 Terreni L, DeSimoni MG. Role of the brain in interleukin-6 modulation. *Neuroimmunomodulation* 1998; **5**: 214–9

125 Traub MM, Rothwell JC, Marsden CD. Anticipatory postural reflexes in Parkinson's disease and other akinetic-rigid syndromes and in cerebellar ataxia. *Brain* 1980; **103**: 393–412

126 Tuite P, Ebbitt B. Dopamine agonists. *Sem Neurol* 2001; **21**: 9–14

127 Tzourio C, Rocca WA, Bretteler MMB, *et al.* Smoking and Parkinson's disease: an age-dependent risk effect? *Neurology* 1997; **49**: 1267–72

128 Vidailhet M, Rivaud S, Goulder-Khouja N, *et al.* Eye movements in parkinsonian syndromes. *Ann Neurol* 1994; **35**: 420–6

129 Vincken WG, Gauthier SG, Dollfuss RE, Hanson RE, Darauay CM, Cosio MG. Involvement of upper-airway muscles in extrapyramidal disorders. A cause of airflow limitation. *N Engl J Med* 1984; **311**: 438–42

130 Vodusek DB. Sphincter EMG and differential diagnosis of multiple system atrophy. *Mov Disord* 2001; **16**: 600–7

131 Vreeling FW, Verhey FR, Houx PJ, Jolles J. Primitive reflexes in Parkinson's disease. *J Neurol Neurosurg Psych* 1993; **56**: 1323–6

132 Wand P, Kuschinsky K, Sontag KH. Morphine-induced muscle rigidity in rats. *Eur J Pharmacol* 1973; **24**: 189–93

133 Weiner WJ. The initial treatment of Parkinson's disease should begin with levodopa. *Mov Disord* 1999; **14**: 716–24

134 Wenning GK, Jellinger KJ, Quinn NP, Poewe WH. An early report of striatonigral degeneration. *Mov Disord* 2000; **15**: 159–62

135 Wenning GK, Seppi K, Scherfler C, Stefanova N, Puschban Z. Multiple system atrophy. *Sem Neurol* 2001; **21**: 33–40

136 leWitt A. Deprenyl's effect at slowing progression of parkinson disability: the DATATOP study. *Acta Neurol Scand* 1991; **84**: 79–86

137 Zesiewicz TA, Hauser RA. Neurosurgery for Parkinson's disease. *Sem Neurol* 2001; **21**: 91–101

138 Zetusky WJ, Jankovic J, Pirozzolo FJ. The heterogeneity of Parkinson's disease: clinical and prognostic implications. *Neurology* 1985; **35**: 522–6

139 Zhang Z-X, Roman GC. Worldwide occurrence of Parkinson's disease; an updated review. *Neuroepidemiology* 1993, **12**: 195–208

140 Zornberg GL, Alexander Bodkin J, Cohen BM. Severe adverse interaction between pethidine and selegiline. *Lancet* 1991; **337**: 246

British Journal of Anaesthesia 89 (6): 917–19 (2002)

BJA

SHORT COMMUNICATIONS

What information do anaesthetists provide for patients?

G. M. M. Thoms[1]*, G. A. McHugh[1] and J. A. Lack[2]

[1]Evaluation and Audit Unit, University Department of Anaesthesia, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL, UK. [2]Department of Anaesthesia, Salisbury Hospital, Salisbury, UK

**Corresponding author*

Background. Information on anaesthesia interventions, plans and risks is needed by patients and carers alike and is a key component of the *Good Practice In Consent* initiative. Existing information materials may under-represent what patients are able to contribute.

Method. UK anaesthetic departments were surveyed on provision of written patient information. The response rate was 66% (177/267).

Results. Fifty-five per cent of respondents reported providing patient information materials for planned surgical admission, mainly on general anaesthesia, regional analgesia and pain. A minority provided information for children and for critical care patients. Few (32%) had sought feedback from patients, and few used existing sources of guidance. Most (85%) wanted improvements, with a four-to-one majority favouring central resources developed by The Royal College of Anaesthetists.

Conclusions. Working in parallel does not give our hospitals excellent, effective patient information materials. Demand exists for The Royal College of Anaesthetists to lead in this area. Working in partnership with patients and taking into account existing written guidance is important but has often been overlooked.

Br J Anaesth 2002; **89:** 917–19

Keywords: anaesthesia, patient information

Accepted for publication: July 30, 2002

Patients and carers need information about interventions and care provided by anaesthetists, including alternatives and risks.[1] Written information for patients underpins two vital processes for achieving patient-centred healthcare: exploration of preferences and making informed choices. It is also central to the Department of Health's drive to strengthen consent. We surveyed anaesthesia departments in the UK, seeking an overview of provision of patient information materials, as the first stage of a Royal College of Anaesthetists' project to evaluate existing patient information and to create new material where necessary.[2]

Previous studies focused largely on the process of developing information materials and on evaluating their quality.[3–6] Developing patient information is a complex process involving appropriate methods for patient involvement and consultation; targeting and dissemination; impact assessment and updating. There can be substantial time and other costs. Evaluations have shown that existing information materials may suffer from incomprehensibility, unavailability, uncertain quality, inappropriateness and lack of balance.[6–7] Petterson found that 10% of patient information materials had demanding readability scores—equivalent to learned articles in medical journals.[7]

Methods and results

In spring 2001, after piloting in two sites and taking into account comments received, we sent our survey instrument to all 267 UK hospitals with an anaesthesia department. Our main objective was to understand the approach at hospital level to patient information, exploring leadership, methods used to reach patients, and processes used to develop, update and assess the impact of information materials. We also explored perceived scope for improvement and the role of The Royal College of Anaesthetists in producing information materials. Finally, we explored the content and range of patient information reportedly provided, focusing on anaesthesia for routine admissions, general,

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

regional and sedation techniques, and certain specific patient groups.

We received 179 questionnaires (two unusable) from the 267 anaesthesia departments surveyed, so our response rate was 66% overall. Results are expressed both as absolute numbers and as percentages of those responding, unless otherwise stated.

Approach at hospital level

Leadership

Most responders (93%, *n*=165) were consultant anaesthetists. Nearly two-thirds of anaesthesia departments (63%, *n*=112) had a named contact for patient information. Occasionally another department (Patient Information; Quality; Risk Management; Communications) was responsible.

Dissemination of information to patients

Of the 177 responders, 50% (*n*=89) reported providing information at pre-admission clinics, 35% (*n*=62) attached information materials to admission letters and 34% (*n*=60) provided information materials to patients at admission; some responders did all three.

Resources used

Guidance used in developing local information materials included: *Anaesthesia Explained: A Patients Guide* (Association of Anaesthetists of Great Britain and Ireland; AAGBI)[8] (*n*=36), *How to write medical information in plain English* (Plain English Campaign)[9] (*n*=5), the DISCERN readability instrument[4] (*n*=3) and other resources (*n*=10).

Piloting and updating

A third of departments (32%, *n*=57) reported seeking patient feedback on the information they provided. Rather fewer departments (21%, *n*=37) went the extra step of formally piloting information materials that they had produced. Approaches to updating varied, with 75 (42%) reporting having updated some of their patient information materials in the previous 2 yr. A quarter of departments (24%, *n*=42) reported having a policy for regularly updating patient information.

Scope for improvement

In the view of most departments (85%, *n*=150), improvements were needed to existing information, and included making it more comprehensive and more available, including more detail, better targeting and better presentation. Most (71%, *n*=126) also commented on what should be produced at national level, the top five suggestions for content being: general anaesthesia (*n*=25), pain relief (*n*=25), safety aspects, spinal analgesia and regional analgesia (*n*=14 in each case). Although 26 respondents argued that patient information materials should always be produced locally, most of those stating a view supported The Royal College of Anaesthetists in producing a central resource (*n*=100). Many wanted this to be produced in a way that allows amendment at local level, for example to include local information.

Content of patient information currently provided

Of the 177 departments surveyed, 55% (98 hospitals) reported providing information of some kind for planned admissions. Patient information with the following content was provided: pain management (*n*=117, 66%), general anaesthesia (*n*=82, 46%), epidural analgesia (*n*=63, 36%), spinal analgesia (*n*=40, 23%), local techniques (*n*=30, 17%) and sedation (*n*=15, 8.5%). Of the 164 hospitals with critical care facilities, information on critical care was provided for relatives by 55% (*n*=90) and for patients by 37% (*n*=60). Most hospitals (133, 75%) reported providing information materials for day-case patients, most of which emphasized general information rather than anaesthetic care.

Chronic diseases

Information materials relating to anaesthesia for patients with chronic diseases were reportedly provided by only 24 (14%) of hospitals. Patient groups covered were those with diabetes (19 hospitals), cardiovascular disease (*n*=8), respiratory disease (*n*=6), renal disease (*n*=6) and haemoglobinopathies (*n*=3).

Children

A substantial minority of the 156 departments that provided a children's anaesthesia service also provided anaesthesia information materials. Children were the target in 44 hospitals, (28% of 156), and parents in 55 hospitals (36% of 152 responding). Some hospitals provide both types of information materials.

Disability

Thirty-nine hospitals reported providing information for patients with disabilities, as follows: hearing impaired (*n*=27); physical disabilities (*n*=23); visual impairment (*n*=6); literacy problems and learning disabilities (*n*=3 each).

Ethnic minorities

Most hospitals (64%, *n*=113) reported having access in principle to linkworkers/interpreters to assist with information for patients from ethnic minorities. However, staff were in such short supply that 58% (*n*=102) hospitals relied largely on English-speaking relatives. Just over half (*n*=92) reported that they did not provide any written anaesthetic information for patients from ethnic minorities. A minority (9%, *n*=16) had information leaflets in several languages.

Jehovah's witnesses

Most hospitals (80%, *n*=142) reported having no suitable information available. Responses included: special consent form (*n*=13), information booklet (*n*=10), link person (*n*=2), local policy (*n*=2) and *Management of Anaesthesia for Jehovah's Witnesses* (AAGBI)[10] (*n*=1).

Comment

Patient-centred healthcare is high on the UK government's modernization agenda for health. Excellent patient information will be a prerequisite. Our study reflected reported practice on patient information in 66% of UK anaesthesia departments. If, as is likely, responders gave more attention to this topic than non-responders, then our results may overstate the extent of information provision.

Many departments produced their own information materials but did not involve patients in the production of these materials, nor did they pilot materials. Although sound guidance exists to assist clinicians in developing patient information materials,[3–5] very few anaesthesia departments had made use of it. Some topics are relatively well served with information materials, for example pain management. However, some important topics (e.g. spinal analgesia) and some patient groups (e.g. children) were not served in most hospitals. Information on anaesthesia for patients with special needs (e.g. diabetes) was in particularly short supply. Many responders stressed that existing patient information should be improved upon.

Acknowledgements

Thanks to the many departments of anaesthesia who contributed, and to the Patient Information Working Group and officials of The Royal College of Anaesthetists.

References

1 NHS Management Executive. A guide to consent for examination and treatment. London: NHS Management Executive, 1990
2 Lack JA, Craggs L. Are your patients informed about anaesthesia? *Bull R Coll Anaesthesists* 2001; **6**: 259
3 Duman M, Farrell C. *The POPPI Guide: Practicalities of Producing Patient Information.* London: King's Fund, 2000
4 Charnock D, Shepperd S, Needham G, Gann R. DISCERN: an instrument for judging the quality of written consumer health information on treatment choices. *J Epidemiol Community Health* 1999; **53**: 105–11
5 National Health and Medical Research Council. How to present the evidence for consumers: preparation of consumer publications. Australia: NHMRC, 2000
6 Mumford ME. A descriptive study of the readability of patient information leaflets designed by nurses. *J Advanced Nursing* 1997; **26**: 985–91
7 Petterson T. How readable are the hospital information leaflets available to elderly patients? *Age Ageing* 1994, **23**. 14–16
8 Association of Anaesthesists of Great Britain and Ireland. *Anaesthesia Explained: A Patients Guide* www.aagbi.org.uk
9 Plain English Campaign. *How to Write Medical Information in Plain English.* www.plainenglish.co.uk/medicalguide.html
10 Association of Anaesthesists of Great Britain and Ireland. *Management of Anaesthesia for Jehovah's Witnesses.* London: AAGBI, 1999

British Journal of Anaesthesia 89 (6): 919–22 (2002)

Lactic acidosis in the rectal lumen of patients with septic shock measured by luminal equilibrium dialysis

V. Due[1], J. Bonde[1], K. Espersen[2], T. H. Jensen[2] and A. Perner[2]*

[1]Department of Anaesthesia and Intensive Care, Herlev Hospital, University of Copenhagen, DK-2730 Herlev, Denmark. [2]Department of Anaesthesia and Intensive Care, Rigshospitalet, University of Copenhagen, DK-2100 Copenhagen, Denmark

**Corresponding author*

Background. Gut ischaemia may contribute to morbidity in sepsis, but little is known about the metabolic state of the gut mucosa in such patients.

Methods. Nine patients with abdominal septic shock treated with norepinephrine, and ten healthy subjects, were subjected to equilibrium dialysis with a rectal balloon. pH, $P\text{CO}_2$ and concentrations of L-lactate were measured by auto-analyser.

Results. In rectal dialysis fluid from patients with septic shock, acidosis was present (pH 7.23, 95% CI 7.11–7.36) and concentrations of L-lactate were approximately five times greater than controls (2.5–5.8 vs 0.5–1.2 mmol litre^{-1}). The lactate concentration was related to the dose of norepinephrine ($P<0.001$). In contrast, values of dialysate $P\text{CO}_2$ did not differ significantly between patients and controls (6.4–11.0 vs 8.9–13.8 kPa).

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Conclusions. The results suggest that, either lactic acidosis in rectal mucosa is related to shock severity, or that norepinephrine causes mucosal ischaemia. In any case, metabolic dysfunction is present in the rectal mucosa in patients with abdominal septic shock treated with norepinephrine.

Br J Anaesth 2002; **89**: 919–22

Keywords: acid–base equilibrium, acidosis; gastrointestinal tract, intestinal mucosa; infection, sepsis

Accepted for publication: July 21, 2002

In septic shock, gut ischaemia may contribute to morbidity and this feature may be remediable in septic patients.[1] However, very little is known about the metabolism of the gut in human septic shock.

We set out to measure pH, $P\text{CO}_2$ and concentrations of L-lactate in the gut of patients with septic shock and healthy subjects. Luminal equilibrium dialysis is a valid, non-invasive method for the estimation of extracellular concentrations of small molecules (<12 kDa) in rectal mucosa.[2] Animal studies show that measurement of mucosal lactate by luminal microdialysis is a valid method by which to assess intestinal ischaemia.[3]

Methods and results

Participants

After approval by the regional ethics committee and with informed written consent, we studied nine patients with peritonitis (six had intestinal perforation and three acute pancreatitis) and established septic shock (>24 h), and ten healthy volunteers.

Septic shock was defined as the presence of a positive bacterial culture from the blood or the peritoneal cavity and the need for infusion of norepinephrine (>0.04 μg kg^{-1} min^{-1}) to maintain a mean arterial pressure (MAP) >70 mm Hg. We did not include patients with any of the following conditions: (i) any changes in cardiovascular treatment in the preceding 2 h, (ii) systemic hypoxia ($P\text{a}_{\text{O}_2}$<8 kPa), (iii) abnormal rectum or left colon, (iv) active gastrointestinal bleeding, or (v) an intra-abdominal pressure >20 mm Hg. All patients had been resuscitated with i.v. fluids before the study using Dextran 60 (Macrodex®; Pharmacia-Upjohn, Uppsala, Sweden) and isotonic saline until the arterial pressure was stable, after which another 1000–2000 ml of fluid were given. Blood was given if the haemoglobin concentration was <5 g dl^{-1}. If oliguria was present, dopamine was infused at 4 μg kg^{-1} min^{-1} (four patients). All patients received systemic antibiotics, selective digestive decontamination (except three patients) and enteral nutrition (except one). Three patients had a pulmonary artery catheter in place during the study. All of these patients had a cardiac index >3 litre min^{-1} m^{-2}, a pulmonary capillary wedge pressure >16 mm Hg and a systemic vascular resistance index <1000 dyn s cm^{-5} m^{-2}.

Luminal equilibrium dialysis

pH, $P\text{CO}_2$ and concentrations of L-lactate in rectal mucosa were measured by luminal equilibrium dialysis as previously described.[2] Bags of dialysis tubing (semipermeable cellulose, cut-off 12 kDa; Sigma, St Louis, MO, USA) were closed over 5 cm of Tygon® tube (Cole-Parmer Instruments Company, Vernon Hills, IL, USA) with a three-way stopcock at the distal end for airtight sampling. Bags were filled with 4 ml of Dextran 40 10% in isotonic saline (Rheomacrodex®; Pharmacia-Upjohn) and placed in the rectal lumen for 4 h, which was the time required for 100% equilibrium of eicosanoids *in vivo*.[2] Incubation of dialysis bags for 2 h in a saline bath containing 1 mmol litre^{-1} L-lactate (Sigma) at 37°C was sufficient for 100% equilibrium of L-lactate. pH, $P\text{CO}_2$ and L-lactate were measured by auto-analyser (ABL 625, Radiometer, Copenhagen, Denmark). As D-lactate may be produced by luminal bacteria, saline solutions containing 1, 10 and 100 mmol litre^{-1} D-lactate (Sigma) were analysed in the ABL 625, but D-lactate was undetectable (n=3).

Statistics

Normal distribution of the variables was tested with the Kolmogorow–Smirnov statistics and the Levine test was used to test for equal variance. Data were analysed by Student's t-test for unpaired or paired variables, or linear regression analysis where appropriate.[4] P-values <0.05 (2-tailed) were considered significant.

Results

In dialysis fluid from the patients with septic shock, acidosis and increased concentrations of L-lactate were observed compared with values in fluid from healthy subjects (Table 1). In septic patients, the mean concentration of L-lactate in dialysis fluid was 70% greater than in arterial blood (P=0.03, Table 1), and there was no correlation between the two values (P=0.27). In contrast, dialysate

Table 1 Characteristics and metabolic values in arterial blood and rectal dialysis fluid in patients with abdominal septic shock and healthy subjects Data are mean (SD or range) or number of patients (%). *Values from seven patients, as air-contamination occurred in dialysates from two patients

	Septic patients (n=9)	**Healthy subjects** (n=10)	t-test P
Age (yr)	56 (38–72)	26 (23–32)	0.0001
Mortality (%)	45	–	
SAPS II	43 (9)	–	
MAP (mm Hg)	80 (9)	–	
HR (beat min^{-1})	103 (19)	–	
Arterial blood			
pH	7.34 (0.05)	–	
P_{CO_2} (kPa)	5.8 (0.8)	–	
P_{O_2} (kPa)	11.9 (1.4)	–	
L-lactate (mmol $litre^{-1}$)	2.4 (1.3)	–	
Rectal dialysate			
pH	7.23 (0.15)*	7.46 (0.15)	0.01
P_{CO_2} (kPa)	8.7 (2.8)*	1.3 (3.2)	0.34
L-lactate (mmol $litre^{-1}$)	4.1 (2.2)	0.8 (0.5)	0.0002

HR=heart rate, MAP=mean arterial pressure; SAPS II=simplified acute physiology score II.

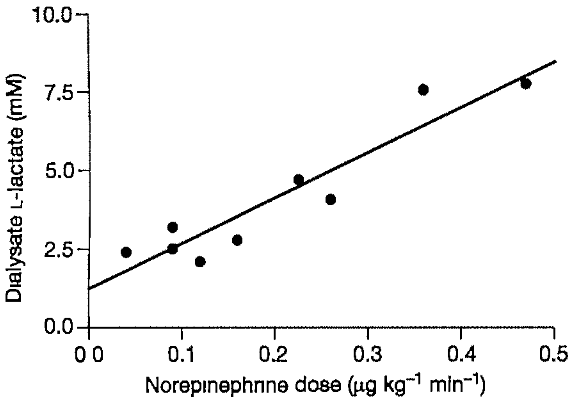


Fig 1 Relationship between rectal dialysis fluid concentration of L-lactate and the dose of norepinephrine in patients with abdominal septic shock. r^2=0.89; P=0.0001 by linear regression analysis.

concentrations of L-lactate correlated with the dose of norepinephrine (Fig. 1, r^2=0.89; P=0.0001). The dose of norepinephrine was not related to systemic values of L-lactate (P=0.48).

Comment

Our results show lactic acidosis in the rectal lumen of patients with abdominal septic shock. Lactic acidosis may represent anaerobic glycolysis from hypoperfusion of rectal mucosa. Although sympatomimetics can cause systemic lactic acidosis through aerobic glycolysis, this has not been seen during infusion of norepinephrine,[5] as was used in the present study. In support of this, systemic values of L-lactate were not related to norepinephrine dose in our patients, but the regression analyses of the present study have a high risk of a type II error. In addition to being markers of metabolism, acidosis[6] as well as lactate[7] can cause cellular dysfunction leading to increased intestinal permeability and increased morbidity in septic shock.

Rectal equilibrium dialysis may be a simple, non-invasive method to measure markers of metabolism in gut mucosa in critically ill patients. The 4 h of equilibration used in the present study may hamper its clinical use. However, it is possible that equilibrium can be obtained earlier or that non-equilibrium dialysis with a shorter time of exposure can detect clinically relevant differences. Future studies should address these questions as well as the effects of age, dopamine, antibiotics, enteral nutrition and fluid management.

The high values of P_{CO_2} observed in the rectal lumen of both patients and healthy subjects suggest that carbon dioxide may come from bacterial metabolism. Alternatively, weak acids in faeces may be buffered by HCO_3^-, which is secreted into the lumen by rectal epithelial cells. Consequently, any change in bacterial number or metabolism or epithelial secretion of HCO_3^- could affect P_{CO_2}, pH, or both and complicate the interpretation of these values. In the gastric mucosa, an increased luminal–arterial P_{CO_2} gap may indicate regional hypoperfusion. We did not determine arterial P_{CO_2} in the healthy subjects, so comparison between the groups is not possible. Bacterial metabolism may also generate D-lactate, but this was not detectable by the auto-analyser used in the present study. This suggests that bacterial metabolism did not contribute to the high dialysate lactate observed in septic patients.

The observed relationship between dialysate L-lactate and norepinephrine dose suggests that mucosal L-lactate is related to shock severity, which may be indicated by the dose of norepinephrine. Alternatively, norepinephrine treatment may itself cause mucosal ischaemia. In any case, metabolic dysfunction is present at the rectal–mucosal barrier in patients with abdominal septic shock treated with norepinephrine.

References

1 Landow L, Andersen LW. Splanchnic ischaemia and its role in multiple organ failure. *Acta Anaesthesiol Scand* 1994; **38**: 629–39

2 Lauritsen K, Laursen LS, Bukhave K, Rask-Madsen J *In vivo* profiles of eicosanoids in ulcerative colitis, Crohn's colitis, and Clostridium difficile colitis. *Gastroenterology* 1988; **95**: 11–17

3 Tenhunen JJ, Kosunen H, Alhava E, Tuomisto L, Takala JA. Intestinal luminal microdialysis: a new approach to assess gut mucosal ischemia. *Anesthesiology* 1999; **91**: 1807–15

4 Kuo J, Fox E. Sigma Stat® Manual. Microcomputer Tools for Scientist. Revision SSD-1.0. Augsburg: Jandel Scientific, 1992

5 Totaro RJ, Raper RF Epinephrine-induced lactic acidosis following cardiopulmonary bypass. *Crit Care Med* 1997; **25**: 1693–9

6 Menconi MJ, Salzman AL, Unno N, *et al.* Acidosis induces hyperpermeability in Caco-2BBe cultured intestinal epithelial monolayers. *Am J Physiol* 1997; **272**: G1007–21

7 Plum J, Razeghi P, Lordnejad RM, *et al.* Peritoneal dialysis fluids with a physiologic pH based on either lactate or bicarbonate buffer-effects on human mesothelial cells. *Am J Kidney Dis* 2001; **38**: 867–75

British Journal of Anaesthesia **89** (6): 922–4 (2002)

Bacterial contamination of epidural needles after multiple skin passes

C. Orlikowski[1]*, P. M. Majedi[1] and A. D. Keil[2]

[1]Department of Anaesthesia and [2]Department of Microbiology, King Edward Memorial Hospital for Women, Bagot Road, Subiaco, WA 6008, Australia

**Corresponding author: Department of Anaesthetics, Royal Hobart Hospital, 48 Liverpool Street, Hobart, Tasmania 7001, Australia*

Background. Infection and epidural abscess are important complications of epidural analgesia. Difficult insertion may be associated with an increased risk of bacterial contamination of the epidural needle or catheter.

Methods. Bacterial contamination of epidural needles and trocars after difficult epidural insertion, defined as two or more skin passes, was assessed in 38 obstetric and ten gynaecological patients.

Results. There was no bacterial growth on any of the 48 epidural needles or trocars despite the mean (range) insertion time being 20 (10–30) min and the number of insertion attempts being 3 (2–4).

Conclusions. Difficult epidural insertion is not associated with an increased risk of needle contamination and is therefore an unlikely source of epidural infection.

Br J Anaesth 2002; **89**: 922–4

Keywords: anaesthetic techniques, epidural; equipment, needles; infection, bacterial

Accepted for publication: June 20, 2002

Infection and epidural abscess is an important complication after epidural analgesia. A recent prospective multi-centre Danish survey reported nine epidural abscesses out of 17 372 epidurals, or an incidence of one in 1930 patients.[1] Sterility at time of siting the epidural is critical to prevent the introduction of bacteria with the passing of the epidural needle. A prospective study has recently identified an overall 16.7% incidence of bacterial contamination of spinal needles (n=114) and 25% contamination of epidural needles (n=20) after a single pass of the needle in elective orthopaedic or urological surgery.[2]

As a result, we postulated that difficult epidural catheter insertion might be associated with an even higher incidence of bacterial contamination of epidural needles. We undertook a study to establish the incidence of epidural needle bacterial contamination after difficult epidural placement

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Table 1 Distribution of weight, ASA status and distance to epidural space

ASA	n	Distance to epidural space (cm)	n	Weight (kg)	n
I	16	3	1	<50	2
II	25	4	7	50–75	18
III	6	5	20	76–100	20
IV	1	6	9	101–125	6
		>6	11	>125	2

and to determine whether the incidence of bacterial contamination increased with difficulty.

Methods and results

Approval for the study was obtained from the Hospital Research Committee. Epidural needles and trocars after difficult epidural insertion in 38 obstetric and ten gynaecological patients were cultured. Difficult epidural insertion was defined as two or more skin passes (i.e. the epidural needle was removed from the patient's back and re-inserted, either through the original skin puncture or through a new puncture).

Standard aseptic technique at our institution for the siting of epidurals included face-mask, hat, sterile gown and gloves. The skin was cleaned using a red-tinted chlorhexidine 0.5% in alcohol 70% solution applied at least three times and allowed to dry. Disposable epidural Abbott kits (Abbott Ireland, Sligo, Republic of Ireland) were used at the time of study.

After any difficult epidural insertion, the epidural needle and trocar were placed in separate sterile containers by the anaesthetist and sent to the laboratory, where 1 ml of sterile BBL trypticase soy broth (Becton Dickinson Biosciences, Lane Cove, Australia) was added to each of the needle and trocar tip containers. After vigorous vortexing for 30 s, 0.5 ml was removed and inoculated *in toto* onto a 5% defibrinated horse blood Columbia agar plate (Oxoid, West Heidelberg, Australia). After drying in air, plates were incubated aerobically with additional carbon dioxide 5% at 35°C for 24 h and for a further 24 h if no growth was then observed. A total of 48 epidural needles and trocars were studied after 38 lumbar and ten thoracic epidurals. Further data is shown in Table 1.

The mean (range) number of attempts was 3 (2–4) and time of insertion was 20 (10–30) min. At the time of insertion, four patients were receiving antibiotics for surgical reasons. There was no bacterial growth on any of the epidural needles or trocars (95% CI for the incidence of bacterial contamination 0–7.4%).

Comment

Despite multiple skin passes and difficult insertions, we were unable to demonstrate any bacterial growth. This is in marked contrast to the overall 17.9% incidence of contamination of mostly spinal needles, which were sited with a single pass in another study.[2]

The most likely explanation for our findings may be attributable to the different methodologies used. In the study by Raedler and colleagues,[2] the tryptic soy broth used to rinse the needles was incubated for 24 h before the plating out onto Columbia blood agar. This methodology is sensitive in detecting, via growth amplification, any viable organisms present on the needles from any source, and may include skin organisms acquired at the time of skin passage during placement of the block, or contamination of the needle subsequent to its removal. Another disadvantage of this methodology is that it does not allow for any quantitative estimation of the contaminating bacterial inoculum, as both low and high initial bacterial inoculums will result in the same positive broth culture result.

In contrast, the soy broth used to rinse the needles was plated out directly in our study. This allows for quantitative assessment of the bacterial contamination. In studies of intravascular catheter-associated infections, there is good evidence that both local and bloodstream infection is related to bacterial load as determined by semi-quantitative[3] and quantitative methods.[4] A similar situation is likely to be applicable to epidural-related infections and thus a quantitative culture method may be preferable.

In the study of Raedler and colleagues,[2] there was mention of hats, sterile gloves and drapes, but not of sterile gown and face-mask. The absence of these may increase the risk of bacterial contamination which, coupled with the culture methods used, may have resulted in their high rate of bacterial contamination. The risk of bacterial contamination when not using a face-mask is highlighted by a case report where the bacteria cultured from an epidural abscess was exactly the same as that found in the nose of the anaesthetist who performed the procedure.[5]

Also, the iodine 10% solution used in the Raedler study may not be the most effective antiseptic. In a study of 69 patients undergoing back surgery, the operative field was prepared with three-layer application of either chlorhexidine 0.5% in alcohol 80%, or povidone-iodine 10%.[6] Excised skin specimens were cultured with an incidence of 5.7% positive culture in the chlorhexidene group compared to 32.4% incidence in the iodine sample ($P<0.01$).

In conclusion, provided rigorous skin asepsis is used, an increase in number of skin passes, or time taken establishing epidural anaesthesia, does not appear to be risk factors for bacterial contamination of epidural needles.

References

1 Wang LP, Hauerberg J, Schmidt JF. Incidence of spinal epidural abscess after epidural analgesia. *Anesthesiology* 1999; **91**: 1928–36

2 Raedler C, Lass-Florl C, Puhringer F, Kolbitsch C, Lingnau W, Benzer A. Bacterial contamination of needles used for spinal and epidural anaesthesia. *Br J Anaesth* 1999, **83**: 657–8

3 Maki DG, Weise CE, Saradin HW. A semiquantitative culture method for identifying intravenous-catheter-related infections. *New Engl J Med* 1977; **296**: 1305–9

4 Fan ST, Teoh-Chan CH, Lau KF. Evaluation of central venous catheter sepsis by differential quantitative blood culture. *Eur J Clin Microbiol Infect Dis* 1989, **8**: 142–4

5 North JB, Brophy BP. Epidural abscess: a hazard of spinal epidural anaesthesia. *Aust NZJ Surg* 1979; **49**: 484–5

6 Sato S, Sakuragi T, Dan K. Human skin flora as a potential source of epidural abscess. *Anesthesiology* 1996; **85**: 1276–82

British Journal of Anaesthesia 89 (6): 925–7 (2002)

BJA

CASE REPORTS

Intrathecal morphine overdose during combined spinal–epidural block for Caesarean delivery

M. Cannesson, N. Nargues, B. Bryssine, R. Debon, E. Boselli and D. Chassard*

Service d'Anesthésie-Réanimation, Hôpital de l'Hôtel-Dieu, F-69002 Lyon, France
**Corresponding author*

We describe a 25 mg intrathecal morphine overdose during a combined spinal–epidural block for a Caesarean delivery. Naloxone infusion (5.24 mg over 24 h) was started prior to the patient becoming symptomatic and almost immediately after the overdose. Invasive therapeutics such as mechanical ventilation were avoided.

Br J Anaesth 2002; **89**: 925–7

Keywords: anaesthetic techniques, regional; analgesics opioid, morphine; complications, overdose

Accepted for publication: July 8, 2002

Since it was introduced by Brownridge in 1981,[1] combined spinal–epidural block has gained popularity as a standard regional technique for Caesarean delivery. Opioids associated with hyperbaric bupivacaine 0.5% 2.5 ml (12.5 mg) are commonly chosen for subarachnoid administration because they provide rapid and profound analgesia. Secondarily, epidural block is used to extend spinal analgesia and to treat postoperative pain.

Occasional intrathecal morphine overdoses have been reported, but most of them were described in patients chronically exposed to these drugs and for whom tolerance is well known.[2 3]

However, there are few reports in the literature describing the perioperative course of an opioid intrathecal overdose.[4–6] These previous cases occurred in patients undergoing orthopaedic surgery and where cerebro-spinal fluid removal, or mechanical ventilation, or both were performed. Our report details the successful treatment of intrathecal morphine 25 mg overdose that did not require such invasive managements during a combined spinal–epidural block for a Caesarean delivery.

Case report

The patient was a healthy 31-yr-old, gravida 7, para 4, at 39 weeks gestation, 156 cm and 75 kg parturient with a singleton pregnancy. She had an uncomplicated prenatal course and was scheduled for elective Caesarean delivery because of a contracted pelvis, for which she had already undergone four Caesarean sections under spinal anaesthesia.

The spinal puncture was performed by the midline approach at the L2–L3 interspace with the patient in the sitting position. The anaesthetist injected fentanyl 30 μg and 2.5 ml of what was thought to be sterile hyperbaric bupivacaine 0.5% through the spinal needle. Immediately after the injection, the solution was identified as morphine 10 mg ml^{-1} intended to fill the reservoir of the i.v. patient-control postoperative analgesia device. The ampoules were visually checked, but the similar appearance of bupivacaine and morphine ampoules may have been responsible for the misidentification. Thus, the patient received 25 mg morphine intrathecally instead of bupivacaine. Fifteen minutes after the event, she did not report any change in temperature sensation and had no motor block. Nevertheless, the epidural block was performed (lidocaine 2% with epinephrine 1:200 000 10 ml, lidocaine 2% 10 ml) and the patient was immediately placed in supine position. Respiratory rate was 12–14 bpm while breathing 6 litres min^{-1} 100% oxygen and she was haemodynamically stable (arterial pressure 115/62 mm Hg, heart rate 82 beat min^{-1}). An i.v. naloxone infusion at 80 μg h^{-1} was initiated after a loading dose of 0.4 mg and vital signs were checked every 5 min.

A healthy, 3800 g boy with Apgar scores of 9 and 10 at 1 and 5 min, was delivered 90 min after the event. Following informed consent from the mother, plasma concentration of morphine was measured in the baby immediately after the

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Table 1 Plasma concentrations of morphine in the mother and in the baby after intrathecal morphine 25 mg

Time (h)	Plasma concentration of morphine in mother (ng litre^{-1})	Plasma concentration of morphine in baby (ng litre^{-1})
T_0	5.0	5.2
T_0+4	6.0	
T_0+8	6.3	
T_0+12	2.8	
T_0+16	2.0	
T_0+20	2.0	
T_0+24	2.0	

delivery (mass spectrometry, venepuncture sample) and in the mother 15 min after the injection and 4, 8, 12, 16, 20 and 24 h after the event (Table 1).

During surgery, transient hypotension responded to i.v. ephedrine 9 mg. Immediately after the end of the Caesarean section, the patient was admitted to the post-anaesthesia care unit, where arterial pressure, heart rate, respiratory rate, oxygen saturation, nausea, itching, vomiting, sedation score (0=conscious, 1=somnolent, 2=very somnolent, 3=confused, 4=comatose) and visual analogue self-rating scale (0=no pain, 10=worst pain imaginable) were checked every 15 min. There was no residual nerve block post-natally.

Three hours after the injection of morphine, and because of a respiratory rate of 8 bpm and somnolence (sedation score 2), naloxone i.v. infusion was increased to 200 µg h^{-1}. This resulted, 20 min later, in an increased respiratory rate (10–12 bpm) and decreased sedation. At the same time, it was realized that the morphine ampoule was not sterile, and prophylactic antibiotic treatment was initiated using methicillin 1 g/8 h and ciprofloxacin 200 mg/12 h initially i.v., then orally after 48 h. It was stopped on day 7.

Six hours after the end of the Caesarean section, the patient was admitted to the intensive care unit where arterial pressure, heart rate, respiratory rate, oxygen saturation, nausea, itching, vomiting, sedation score and visual analogue self-rating scale were checked every hour.

During the following 24 h the patient's respiratory rate was normal (lower respiratory rate 8 bpm), she was haemodynamically stable (lower arterial pressure 100/65 mm Hg, higher arterial pressure 141/72 mm Hg) and did not vomit. Sedation score was never greater than 2. She complained of mild pruritus and nausea that responded to i.v. metoclopramide. Urinary catheter was removed on day 1. The patient never reported a visual analogue score of more than six. Pain was controlled easily with proacetaminophen 2 g/6 h. Naloxone infusion was discontinued 24 h after its introduction (arterial pressure 120/80 mm Hg, heart rate 75 beat min^{-1}, respiratory rate 15 bpm, oxygen saturation 98% while breathing room air). She received a total of 5.24 mg naloxone i.v. over the 24 h acute phase.

The patient spent 24 h in the intensive care unit and was discharged to home on day 8. Three months after the event, no signs of meningitis or fever were reported.

Discussion

Accidental massive overdoses of opioids have been reported in various settings, including dysfunction of a patient-controlled analgesia device,[7] and during epidural[8] or intrathecal anaesthesia.[2–6] In our patient, the event was because of an accidental intrathecal morphine injection because of misidentification of drug ampoules. The similar appearance of hyperbaric bupivacaine 0.5% and morphine 10 mg ml^{-1} ampoules may have been responsible for this event. However, the anaesthetist should have checked the drugs, which were prepared by a nurse before injection.

Depending on route of administration, excessive doses of opioids may result in a variety of adverse outcomes, including hypothermia, myoclonic seizures, pulmonary oedema, respiratory depression, coma and death.[9 10]

Intrathecal morphine overdoses in patients who were not chronically exposed to this drug have been reported with morphine doses ranging from 5 to 15 mg.[4–6] These previous reports discussed the management of patients who received less opioid than our patient. Kaiser and Bainton[6] have described success in treating a 5 mg intrathecal injection of morphine after 4 h by the removal of 50 ml of cerebro-spinal fluid from the lumbar area and its replacement with saline. Pomonis and colleagues[5] reported four cases of intrathecal morphine overdoses (15 mg), that occurred in patients undergoing orthopaedic operations under spinal anaesthesia and who necessitated mechanical ventilation despite naloxone infusion (the authors did not report the dose of naloxone). A third report,[4] described an 8 mg intrathecal morphine overdose that did not require mechanical ventilation, probably because of naloxone infusion (9.6 mg over 24 h). The common finding among these three reports is the late recognition of the intrathecal morphine overdoses (1.5–4 h after the event). In our report, naloxone infusion was begun prior to the patient becoming symptomatic and nearly immediately after the morphine injection (15 min). That may explain the success of this non-invasive treatment. Nevertheless, this should be accomplished with small incremental doses to avoid the severe hypertension, dysrhythmias, and pulmonary oedema that are presumably a result of the rapid increases in sympathetic tone that may accompany the sudden return of pain when opioid effects are antagonized too rapidly.[11]

However, in massive intrathecal morphine overdoses (≤250 mg) it is important to consider more invasive treatments.[2 3] Groudine and colleagues,[3] describing a 250 mg intrathecal morphine overdose in a patient chronically exposed to this drug, suggest that attempts to remove as much drug as possible from the cerebro-spinal fluid by aspiration and, if necessary, irrigation should be started immediately. This may avoid direct neurotoxicity of morphine that seems to be responsible for myoclonus unresponsive to i.v. naloxone.[9]

Myoclonus has been experimentally induced in rats[12] and was reported during massive intrathecal morphine overdoses despite naloxone treatment.[3] It is interesting to observe that myoclonus did not occur in our patient despite intrathecal morphine 25 mg.

Sixteen hours after the event, plasma concentrations of morphine were no longer detectable (Table 1). However, ventilatory response does not seem to be correlated with plasma concentrations of morphine after intrathecal injection.[13]

References

1 Brownridge P. Epidural and subarachnoid analgesia for elective Caesarean section *Anesthesia* 1986, **36**: 70

2 Sauter K, Kaufman HH, Bloomfield SM, *et al.* Treatment of high-dose intrathecal morphine overdose. *J Neurosurg* 1994; **81**: 143–6

3 Groudine SB, Cresanti-Dakins C, Lumb PD. Succesful treatment of a massive intrathecal morphine overdose. *Anesthesiology* 1995; **82**: 292–5

4 Perrot G, Muller A, Laugner B. Accidental overdose of intrathecal morphine. Treatment with intravenous naloxone alone. *Ann Fr Anesth Reanim* 1983; **2**: 412–14

5 Pomonis SP, Economacos G, Costopanajiocoy SP Overdose of intrathecal morphine. *Anesthesia* 1986; **41**. 670

6 Kaiser KG, Bainton CR. Treatment of intrathecal morphine overdose by aspiration of cerbrospinal fluid. *Anesth Analg* 1987; **66**: 475–7

7 Kreitzer JM, Kirshenbaum LP, Eisenkraft JB. Safety of PCA devices. *Anesthesiology* 1989; **70**: 881

8 Dahl JB, Jacobsen JB Accidental epidural narcotic overdose. *Anesth Analg* 1990; **70** 321–2

9 Parkinson SK, Bailey SL, Little WL, Mueller JB. Myoclonic seizure activity with chronic high-dose spinal opioid administration. *Anesthesiology* 1990, **72**: 743–5

10 Bruera E. Narcotic-induced pulmonary edema. *J Pain Symptom Management* 1990; **5**: 55–8

11 Flacke JW, Flacke WE, Williams GD. Acute pulmonary edema following naloxone reversal of high-dose morphine anesthesia *Anesthesiology* 1977; **47**: 376–8

12 Shohami E, Evron S. Intrathecal morphine induces myoclonic seizures in the rat. *Acta Pharmacol Toxicol* 1985; **56**: 50–4

13 Bailey PL, Lu JK, Orr JA, *et al.* Effects of intrathecal morphine on the ventilatory response to hypoxia. *N Engl J Med* 2000, **343**: 1228–34

British Journal of Anaesthesia **89** (6): 927–30 (2002)

Management of a known difficult airway in a morbidly obese patient with gross supraglottic oedema secondary to thyroid disease

M. Hariprasad and G. J. Smurthwaite*

Department of Anaesthetics, Hope Hospital (University of Manchester), Salford, Manchester M6 8HD, UK

**Corresponding author. E-mail: susan.leighton@srht.nhs.uk*

We describe the use of awake fibreoptic intubation in the management of a patient with a known difficult airway, who presented with stridor resulting from supraglottic oedema. The aetiological factors contributing to this supraglottic oedema included coexisting thyroid swelling and congestive cardiac failure. Options for appropriate airway management in such cases are discussed.

Br J Anaesth 2002; **89**; 927–30

Keywords: airway; complications, oedema; intubation, fibreoptic

Accepted for publication: July 19, 2002

The appropriate management of the airway in otolaryngological surgery is often a challenge. This may be compounded by coexistent medical conditions and local pathology. Awake fibreoptic intubation is one of the methods to be considered to secure a safe, definitive airway in these circumstances. We present a case in which this technique allowed the safe management of a patient with a known difficult airway complicated by obesity, a short neck, thyroid swelling and congestive cardiac failure.

Case report

A 53-yr-old female presented to the accident and emergency department with a 2-week history of increasing stridor. She

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

denied any previous similar episodes. There was no history of dysphagia or exacerbation of stridor at night. There was no evidence of any weight loss in the recent past. She was known to have insulin-dependent diabetes mellitus, hypertension, congestive cardiac failure and carcinoma of the breast.

She had undergone a gastric polypectomy 4 yr before presentation, at which time examination had revealed a grade IV laryngoscopy. Further details of the drugs and method of tracheal intubation used at this time were unavailable. She was given a patient information sheet regarding this finding from the consultant anaesthetist involved, but had misinterpreted the advice given, believing that she should never again receive a general anaesthetic. This had influenced the treatment of her breast carcinoma, for which she was receiving chemotherapy rather than surgery.

On initial examination, inspiratory stridor was clearly audible. She was noted to be a short, very obese lady (body mass index 51) with a short neck, and was extremely anxious. Oxygen saturation measured by pulse oximetry was 95% on air. Arterial blood gas sampling confirmed she was not hypoxic, but was hypercarbic. On a FI_{O_2} of 0.6, pH was 7.405, P_{O_2} 16.7 kPa, P_{CO_2} 6.35 kPa and HCO_3 29.2 mmol litre^{-1}, with a base excess of 4.3. Her heart rate was 90 beats min^{-1} and in regular rhythm, with an arterial blood pressure of 176/96 mm Hg. Auscultation of the chest revealed conducted upper airway sounds. On palpation of the neck, a soft-tissue swelling, firm in consistency, was noted at the anterocentral aspect of the neck. The thyroid cartilage was barely palpable. Intravenous hydrocortisone and nebulized epinephrine were commenced, with slight improvement.

Lateral x-ray films of the soft tissues of the neck (reported by a consultant radiologist) suggested a swelling or mass over the arytenoids and posterior half of the glottis. The epiglottis appeared to be depressed over the glottis. The anteroposterior view showed possible compression and deviation of the trachea to the left. A CT scan or MRI of the neck was unavailable.

Flexible nasendoscopy by an ENT consultant showed excess redundant mucosal thickening with oedema over the arytenoids, which was prolapsing in and out of the glottis during inspiration and expiration. She was commenced on regular dexamethasone and told to have strict voice rest. The patient was admitted to the intensive care unit for airway observation, continuation of oxygen therapy, epinephrine nebulizers and continuous positive airway pressure (if required). Two days later, fibreoptic nasendoscopy was repeated, and although there was some resolution of the oedema a large portion of redundant mucosa was still being drawn into the glottis on inspiration and blown out with expiration. As her condition remained static, it was decided by the ENT surgeons that direct laryngoscopy, microlaryngoscopy and excision of the redundant mucosa were required. In view of her known grade IV intubation risk and the additional problem of soft-tissue overgrowth, early discussion took place between the consultant ENT surgeon and consultant anaesthetist to plan appropriate options. The main concerns from the anaesthetic point of view were her obesity, stridor at rest and the neck swelling, aside from the problems caused by her medical co-morbidity. These factors were complicated by a previous history of difficult intubation.

The safest way to manage the airway for the microlaryngoscopy and debulking was the important consideration. The options considered were: (i) retrograde passage of an epidural catheter with awake intubation, following the catheter as a guide; (ii) tracheostomy under local anaesthetic; (iii) inhalational induction and intubation without a muscle relaxant, with or without pre-placement of a cricothyroid cannula; and (iv) awake fibreoptic intubation.

The first three options would have been difficult considering her short neck, indistinct anatomical landmarks, neck swelling and the risk of losing the airway during inhalational induction. The redundant oedematous tissue could have acted like a ball valve. It was decided that awake fibreoptic intubation was the preferred method.

After a thorough assessment, the consultant ENT surgeon decided she could be discharged home safely with information to return immediately should she deteriorate. The lady was readmitted, as planned, 1 week later. Because of her multiple pathology, it was decided that the surgeon should be ready to perform a tracheostomy whatever the outcome of her airway surgery. She was fully counselled regarding the need for the tracheostomy and the technique of awake intubation via the fibrescope. Premedication with hyoscine 0.4 mg was given i.m. 1.5 h before the procedure. She was also given nebulized epinephrine 5 mg in oxygen during transfer to the operating theatre. After venous access had been secured, the patient was preoxygenated via nasal cannulae in the sitting position, as her size and condition precluded the supine position. Topical cocaine paste (25%) was applied to the nose and the fibrescope was inserted through the right nostril. Topical lidocaine (4%) 2 ml was sprayed into the oropharynx. When the vocal cords became visible, 4% lidocaine 1 ml was sprayed onto the glottis and the fibrescope was introduced gently into the trachea. The procedure was uneventful, though technically very difficult because of the excess tissue (Fig. 1).

The trachea was then sprayed with 4% lidocaine 1 ml before a 6.0 mm armoured tracheal tube was introduced into the trachea, sliding over the fibrescope using a 'railroading' technique. Once the tracheal tube position had been confirmed by capnography, general anaesthesia was induced with oxygen and sevoflurane. The position of the tracheal tube was reconfirmed by the fibrescope before fixation.

During direct pharyngolaryngoscopy after intubation, a view of the supraglottis only was obtained. The supraglottis was very oedematous but there was no obvious tumour seen. It had been decided that a tracheostomy should be performed before supraglottic surgery, in the hope that it

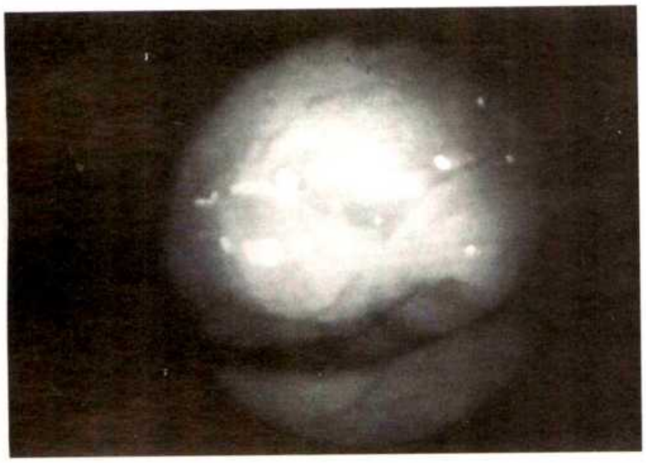


Fig 1 Oedematous supraglottic mucosa.

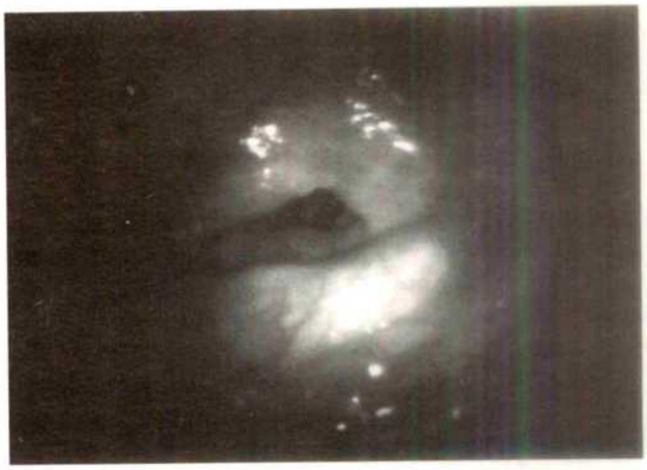


Fig 2 Mucosal oedema resolving after tracheostomy. Note tracheostomy tube *in situ*.

might allow the supraglottic oedema to settle. The mucosal overgrowth might have been worsened by turbulent airflow through the glottis. At tracheostomy, significant thyromegaly was confirmed and a large swelling of the thyroid isthmus was noted. A partial thyroidectomy was performed, resulting in marked decompression of the larynx and trachea. The tracheostomy was technically very difficult. The whole procedure took almost 4 h, resulting in a blood loss of approximately 1500 ml. An awake tracheostomy would have been impossible in this patient. She made a good postoperative recovery, requiring only overnight admission to the intensive care unit before transfer back to the high dependency unit. Histology confirmed the cause of the thyromegaly to be benign, multinodular goitre.

During the following week, repeated flexible nasendoscopy revealed a gradual but sustained resolution of both the oedema and excess mucosa (Fig. 2). The tracheostomy was decannulated at the patient's request and she was discharged 1 month after the operation. The delay in discharge resulted from attempts to improve her congestive cardiac failure and achieve weight control. It is expected that the stoma will remain patent for many months. It would be a relatively simple procedure to dilate the tracheocutaneous tract to re-insert a tracheostomy tube or tracheal tube should she require a general anaesthetic in the future.

Discussion

Appropriate airway management is an essential part of the anaesthetist's role. Airway difficulties are complicated by obesity, a short neck, thyroid swelling or a laryngeal mass. Sharing of the airway with surgeons, as in ENT procedures, makes the tasks more challenging.[1] A strategy needs to be developed in order to anticipate and manage patients with difficult airways. This includes identifying the potential problem, considering different options, and selection of an appropriate plan in the particular scenario of the individual patient. Regular and ongoing discussions with the surgeons regarding the plans are also important. The patient should be informed about the options and the advantages and disadvantages of each. Finally, there should be alternative plans in case of failure of the initial one.

This particular patient had acute stridor as a result of overgrowth of redundant laryngeal mucosa, the cause of which was unclear. Interference of the venous drainage resulting from the thyromegaly was a feasible explanation, but the coexisting congestive cardiac failure made it difficult to ascertain whether the venous congestion was caused only by the thyromegaly. The relatively large thyroid swelling appeared deceptively small on inspection and palpation of the neck, because of the short neck and morbid obesity. However, the fact that the supraglottic swelling started to go down after thyroidectomy and the high intraoperative blood loss would be in keeping with this explanation. The other possible causes of her stridor were a supraglottic tumour and laryngomalacia. A CT or MRI scan of the neck, if available, could have been helpful in identifying the extent of the airway obstruction.

The problems associated with fibreoptic intubation are failure to visualize the glottis, trauma, bleeding and laryngospasm.[2] However, compared with inhalation induction, the risk of losing the airway is minimal. Even sedative premedication can lead to an increase in severity of the stridor, precipitating total obstruction. But withholding sedative premedication can itself pose a problem when the patient is anxious, attempting to breathe through a narrowed airway. Anaesthetizing the airway with local anaesthetics can be suboptimal because of the local pathology.[3] These problems were anticipated, and back-up plans were also considered in detail in case of failure of awake fibreoptic intubation.

Tracheostomy under local anaesthetic was an option considered. A tracheostomy tray was open and ready in the event of any problem arising during fibreoptic intubation, but this could have been difficult because of her short neck, thyroid swelling and the indistinct anatomical landmarks. Retrograde passage of an epidural catheter through the cricothyroid membrane and passage of a tracheal tube over the catheter from above, or introduction of a transtracheal cannula[4] would also have been difficult for the same reasons. Inhalational induction and intubation without muscle relaxants was another option considered, but the risk of losing the airway in a patient with known grade IV laryngoscopy presenting with acute stridor made this option inappropriate. This would have been further complicated as it was uncomfortable for the patient to lie down flat even when awake, because of stridor and her co-morbidity. The only viable option was awake fibreoptic intubation, which the patient tolerated well. Even though this was technically challenging, good planning and communication with the patient and surgeon allowed safe management of the airway in this case.

References

1 Mason RA, Fielder CP. The obstructed airway in head and neck surgery. *Anaesthesia* 1999; **54**: 625–8

2 Shaw IC, Welchew EA, Harrison BJ, Michael S. Complete airway obstruction during awake fibreoptic intubation. *Anaesthesia* 1997; **52**: 582–5

3 Frosh AC, Jayaraj J, Porter S, Almyeda J. Is local anaesthesia actually beneficial in flexible nasendoscopy? *Clin Otolaryngol* 1998; **23**: 259–62

4 Boucek CD, Gunnerson HB, Tullock WC. Percutaneous transtracheal high frequency jet ventilation as an aid to fibreoptic intubation. *Anesthesiology* 1987; **67**: 247–9

British Journal of Anaesthesia **89** (**6**): 930–3 (2002)

Probable allergic reaction to cyclosporin and early formation of thrombi on a pulmonary artery catheter: two unusual complications during bilateral lung transplantation

N. Dalibon[1], M. Stern[2], P. Bonnette[3], G. Dreyfus[4] and M. Fischler[1]*

[1]*Department of Anaesthesiology,* [2]*Department of Pneumology,* [3]*Department of Thoracic Surgery and* [4]*Department of Cardiac Surgery, Hôpital Foch, 40 Rue Worth, F-92151 Suresnes, France*

**Corresponding author. E-mail: m.fischler@hopital-foch.org*

We describe a patient who had two rare complications (a probable allergic reaction to cyclosporin and the early formation of a right atrial thrombus) during bilateral sequential single lung transplantation performed under the one anaesthetic. The thrombus, discovered at the end of the procedure, was then removed under cardiopulmonary bypass. Peroperative trans-oesophageal echocardiography was useful in providing critical diagnostic and therapeutic information.

Br J Anaesth 2002; **89**: 930–3

Keywords: allergy; complications, thrombosis; equipment, catheters; immune response, suppression; measurement techniques, transoesophageal echocardiography

Accepted for publication: July 16, 2002

Bilateral sequential single lung transplantation during one anaesthetic is an option for patients who require double lung replacement.[1] It does not require routine use of cardio-pulmonary bypass because each graft is performed while ventilation and circulation are supported by the contralateral lung; the native lung during the first part of the procedure, and the first transplanted lung during the second. However, in case the haemodynamic condition of the patient deteriorates, cardiopulmonary bypass should always be made ready for use.[1]

We describe two rare complications occurring in a patient during bilateral sequential single lung transplantation: a

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

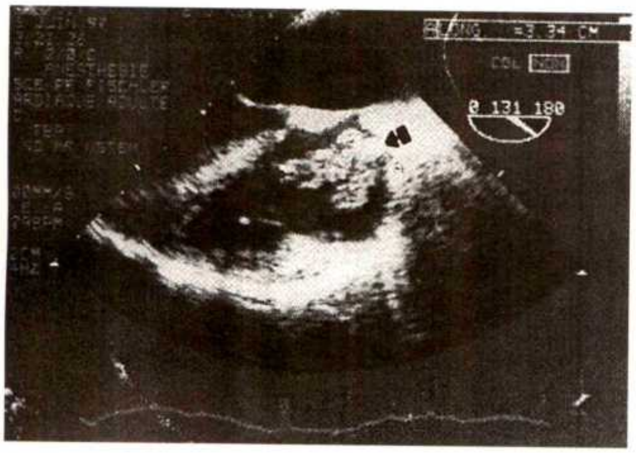


Fig 1 TOE examination using a multiplan probe revealed an echo-dense mass (arrow) bound to the pulmonary artery catheter in the right atrium on a 131° axis of the four-chamber view.

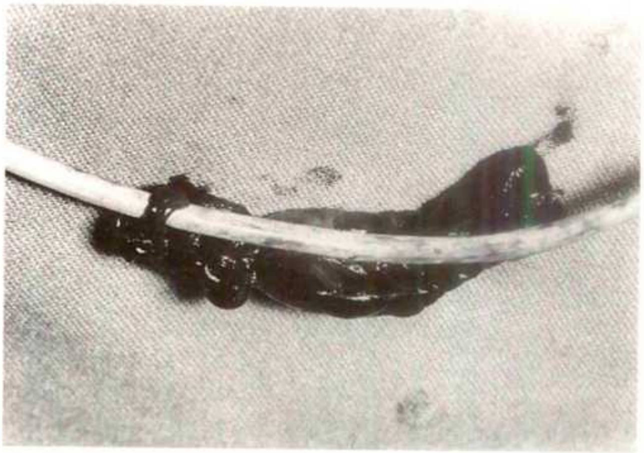


Fig 2 Thrombus bound to the distal end of the pulmonary artery catheter.

probable allergic reaction to cyclosporin, and the formation of a right atrial thrombus discovered at the end of the procedure.

Case report

A 38-yr-old man with cystic fibrosis was scheduled for double lung transplantation. Immunosuppressive agents (cyclosporin 2 mg kg^{-1} and azathioprine 2 mg kg^{-1}) given over 30 min by i.v. infusion were started according to the hospital procedure, immediately before induction of anaesthetic. Simultaneously, a right femoral artery catheter was inserted under local anaesthesia. Suddenly, the patient complained of severe respiratory distress and pulse oximetry showed a rapid decrease in arterial oxygen saturation. The first recorded systolic arterial pressure was 35 mm Hg. Initial management included i.v. injection of epinephrine 1 mg and cessation of the infusion of immunosuppressants. Face mask ventilation with 100% oxygen was quickly followed by tracheal intubation with a double-lumen tracheal tube after bolus administration of etomidate 20 mg and rocuronium 100 mg. Stable haemodynamics were achieved 20 min later, the patient having received two more boluses of epinephrine 1 mg followed by an epinephrine infusion 2 mg h^{-1}. Transoesophageal echocardiography (TOE) showed vigorous, homogeneous contraction of small right and left ventricles without segmental wall motion abnormalities. It ruled out other possible causes of sudden cardiopulmonary distress, especially pneumothorax (there was no right atrial or right ventricle compression), and acute pulmonary embolism (no right ventricular dilatation). The possibility of an anaphylactic reaction either to the latex gloves worn by the anaesthetic team or to the immunosuppressive agents was raised, despite the lack of associated signs such as wheezing or urticaria. We changed to latex-free gloves, and other latex-based products were removed from contact with the patient. As the clinical situation was under control, we decided to reintroduce the i.v. cyclosporin and to complete anaesthesia with the infusion of a large dose of sufentanil (10 µg kg^{-1} over 20 min). Arterial pressure fell within a few seconds of administrating both these drugs to 55/30 mm Hg and required three epinephrine 0.5 mg boluses to correct it. The medical staff discussed the likelihood of an anaphylactic reaction to cyclosporin. We changed the immunosuppressive procedure to high-dose steroids. As usual during lung transplantation, a 8.5-Fr introducer catheter was then placed into the right internal jugular vein, followed by a 7.5-Fr thermodilution, heparin-coated pulmonary artery catheter. The remainder of the anaesthetic procedure was uneventful.

Surgery consisted of bilateral sequential single lung transplantation performed through an anterior bithoracosternotomy incision, as described previously.[1] TOE monitoring continued throughout the surgical procedure to assess haemodynamic status and the arterial and venous vascular anastomoses.[2] At the final perioperative TOE examination, performed before skin closure, an echo-dense mass, 34 mm wide, was detected, attached to the pulmonary artery catheter in the right atrium (Fig. 1). The mass was mobile, entering the right ventricle through the tricuspid orifice during diastole, and returning to the right atrium during systole. It was decided to remove this thrombus. The patient was given heparin 300 IU kg^{-1}. Ascending aortic and right atrial cannulation was employed for cardiopulmonary bypass. The right atrium was opened, and the surgeon cut the extremity of the Swan–Ganz catheter and removed it with the thrombus attached (Fig. 2). The right atrium was closed, the cannulae were removed and the heparin effect was reversed with an infusion of protamine sulphate 300 units over 20 min. At the end of the procedure, we withdrew the proximal part of the Swan–Ganz catheter and replaced it by a triple-lumen central venous catheter.

Postoperative recovery was uneventful. Blood loss in to the chest drains was 980 ml during the first postoperative 24 h. The patient is alive and healthy 24 months after transplantation.

Discussion

Two major complications occurred during this double lung transplantation: a probable allergic reaction to cyclosporin before induction of anaesthesia, and the formation within a few hours of a large right atrial thrombus. TOE ruled out other possible causes of the cardiopulmonary collapse, and facilitated its treatment. It then revealed the atrial thrombus.

The differential diagnoses of the acute cardiopulmonary deterioration before induction of anaesthesia included a tension pneumothorax, massive pulmonary embolism (both complications this patient was at risk of), and anaphylactic shock or another type of adverse drug reaction. The first two diagnoses were ruled out as TOE did not show compression or dilatation of the right cardiac chambers. Moreover, the timing of events suggested that this was a probable allergic reaction to cyclosporin, with immediate hypotension following its administration, and recurrence after reintroduction of the immunosuppressive agent. Proof of the anaphylactic aetiology of the cardiopulmonary collapse is not available, as we did not take blood for histamine, serum tryptase, or complement analyses. Moreover, after recovery, skin prick-tests would not necessarily have led to the diagnosis as immunosuppressive therapy decreases skin reactivity and consequently could have given a false negative result.

Several case reports of life-threatening anaphylactic reactions to i.v. cyclosporin have been reported, one of which resulted in cardiopulmonary arrest.[3] Allergic reactions to i.v. cyclosporin are uncommon (0.1%) and are usually a result of the solvent Cremophor EL (polyoxyethylated castor oil base),[4] which is known to cause anaphylactoid shock. Inappropriate mixing of the solution can lead to a large plasma concentration of Cremophor EL during the initial phase of the infusion; the heavier solvent may fall to the bottom of the mixture and pass through the infusion set first. A recent study reported that cyclosporin and Cremophor EL concentrations could be up to 9-fold higher than intended during the first 10 min of the infusion. This high concentration can be a predisposing factor for anaphylactoid shock.[5] Such a complication requires a change in the immunosuppressive procedure, as in our patient, or the administration of cyclosporin capsules which have been demonstrated to be well tolerated in a patient allergic to standard oral and i.v. solutions of cyclosporin.[4]

The atrial thrombus was attached to the Swan–Ganz catheter. Thrombus formation on a pulmonary artery catheter has been described by several authors.[6 7] In their original description of the double-lumen flow-directed balloon-tipped catheter, Swan and colleagues[8] detailed two patients who had evidence of thrombosis related to the pulmonary artery catheter. In an autopsy study, mural thrombi were found in the right cardiac chambers in approximately one-third of patients.[9] The main mechanism of thrombus formation is dependent on the thrombogenicity of the catheter surface. Thrombus formation starts when a fibrin sleeve forms around an indwelling catheter, exerting a procoagulant effect. Moreover, a hypercoagulable state created by high-dose aprotinin,[10] or administration of epsilon aminocaproic acid,[11] may lead to the formation of thrombi around the catheter within the first hour after insertion. Heparin-coated catheters may prevent or reduce the incidence or severity of such complications. Hoar[12] examined 20 consecutive pulmonary artery catheters in cardiac surgical patients and found adherent thrombi formation on all non-heparin-bonded catheters but none on heparin-bonded catheters. In our case, thrombus formation was diagnosed 10 h after pulmonary artery catheter insertion, in the absence of any precipitating factor (atrial fibrillation, aprotinin administration, blood transfusion, or removal of the introducer sheath).

Any link between an allergic reaction and early thrombus formation is speculative. However, it is well-known that anaphylaxis can trigger a systemic inflammatory reaction in which platelet activating factor and thromboxan A2 are released and induce platelet aggregation and clotting.[13] Moreover, if the reaction to cyclosporin is a result of complement activation by Cremophor EL, this can lead to the release of anaphylatoxin C5a. Again, the end result is platelet aggregation.[14] Another hypothesis might be that clotting is activated during lung transplantation itself. Indeed, a significant rise in concentrations of thrombin/antithrombin III complex and tissue-type plasminogen activator have been reported during the early phase of such surgery.[15]

Perioperative or postoperative diagnosis of an atrial thrombus attached to a central venous catheter or a pulmonary artery catheter using TOE has seldom been reported.[16 17] As the thrombus was discovered during surgery and because of its potential for tricuspid entrapment or pulmonary embolism, we decided to remove it under cardiopulmonary bypass despite the haemorrhagic risk.

This case highlights the importance of simple precautions: monitoring lines and venous access should be established before any drugs are administered. Administration of immunosuppression therapy, or of any drug with potential allergic complications such as aprotinin, must not be concomitant with administration of an anaesthetic drug. This case illustrates how TOE can provide critical diagnostic information and help to manage unstable patients. TOE was useful in two respects: it ruled out right sided atrial and ventricular compression, right ventricular dilatation, right or left ventricular failure, and hypovolaemia when the patient experienced acute cardiorespiratory distress; and it also identified a right atrial thrombus.

Acknowledgement

The authors thank Prof. Laxenaire (Département d'Anesthésie-Réanimation, Hôpital Central, Nancy, France) for her suggestions.

References

1 Bisson A, Bonnette P. A new technique for double lung transplantation. Bilateral single lung transplantation. *J Thorac Cardiovasc Surg* 1992; **103**: 40–6

2 Michel-Cherqui M, Brusset A, Liu N, *et al.* Intraoperative transesophageal echocardiographic assessment of vascular anastomoses in lung transplantation. A report on 18 cases. *Chest* 1997; **111**: 1229–35

3 Friedman LS, Dienstag JL, Nelson PW, *et al.* Anaphylactic reaction and cardiopulmonary arrest following intravenous cyclosporine *Am J Med* 1985; **78**: 343–5

4 Volcheck GW, Van Dellen RG. Anaphylaxis to intravenous cyclosporine and tolerance to oral cyclosporine: case report and review *Ann Allergy Asthma Immunol* 1998; **80**: 159–63

5 Liau-Chu M, Theis JG, Koren G. Mechanism of anaphylactoid reactions: improper preparation of high-dose intravenous cyclosporine leads to bolus infusion of Cremophor EL and cyclosporine. *Ann Pharmacother* 1997; **31**: 1287–91

6 Connors AF Jr, Costale RJ, Farhat NZ, *et al.* Complication of right heart catheterization. A prospective autopsy study. *Chest* 1985; **88**: 567–72

7 Lange HW, Galliani CA, Edwards JE. Local complications associated with indwelling Swan–Ganz catheters: autopsy study of 36 cases. *Am J Cardiol* 1983; **52**: 1108–11

8 Swan HJ, Ganz W, Forrester J, Marcus H, Diamond G, Chonette D. Catheterization of the heart in man with use of a flow-directed balloon-tipped catheter. *N Engl J Med* 1970; **283**: 447–51

9 Ducatman BS, McMichan JC, Edwards WD. Catheter-induced lesions of the right side of the heart. A one-year prospective study of 141 autopsies. *JAMA* 1985; **253**: 791–5

10 Bohrer H, Fleisher F, Lang J, *et al.* Early formation of thrombi on pulmonary artery catheter in cardiac surgical patients receiving high-dose aprotinin. *J Cardiovasc Anaesth* 1990, **4**: 222–5

11 Dentz ME, Slaughter TF, Mark JB Early thrombus formation on heparin-bonded pulmonary artery catheters in patients receiving epsilon aminocaproic acid. *Anesthesiology* 1995; **82**: 583–6

12 Hoar PF, Wilson RM, Mangano DT, et *al* Heparin bonding reduces thrombogenicity of pulmonary-artery catheters *N Engl J Med* 1981; **304**: 993–5

13 de Sousa JR, Palma-Carlos AG. Platelets and hypersensitivity. *J Invest Allergol Clin Immunol* 1995, **5**: 12–17

14 Bjork J, Hugli TE, Smedegard G. Microvascular effects of anaphylatoxins C3a and C5a. *J Immunol* 1985; **134**: 1115–9

15 Gu YJ, de Haan J, Brenken UP, *et al.* Clotting and fibrinolytic disturbance during lung transplantation: effect of low-dose aprotinin. Groningen Lung Transplant Group. *J Thorac Cardiovasc Surg* 1996; **112**: 599–606

16 Goodie DB, Geiser JF. Atrial thrombosis induced by percutaneous central venous catheter: a potential hazard during cardiac surgery diagnosed by intra-operative transoesophageal echo. *Anaesth Intens Care* 1995; **23**: 725–7

17 Martens PR, Driessen JJ, Vandekerckhove Y, *et al.* Transesophageal echocardiographic detection of a right atrial thrombus around a pulmonary artery catheter. *Anesth Analg* 1992; **75**: 847–9

British Journal of Anaesthesia **89** (6): 934–9 (2002)

Correspondence

In vivo effect of haemodilution with saline on coagulation

Editor—As the influence of i.v. fluids on the coagulation system is of importance and also sustains the discussion on optimal fluid therapy, we would like to comment on the results reported by Ng and colleagues[1] and the suggestions presented in the accompanying editorial.[2] The study design chosen by Ng and colleagues[1] to investigate coagulation and haemodilution might eliminate the influence of tissue trauma provoked by surgery, but is not 'without the effect of any confounding variables'.[2]

First, the ratio of blood withdrawn:replacement with normal saline was 1:2, which suggests that the haemodiluted patients were hypovolaemic rather than haemodiluted. Second, all study subjects were patients with malignant disease, who are known to exhibit some state of hypercoagulability because of their underlying disease. Third, the shortening of the reaction time (r-time) by 30% and the coagulation time (k-time) by 36–45% was statistically different from the controls, but they also showed prolongation of the r- and k-times, although no intervention occurred. The question arises as to whether such changes are relevant *in vivo*, as they might be explained as an *in vitro* phenomenon attributable to sedimentation of red cells in the thrombelastograph (TEG) cup. Uraemic patients have been shown to have an increased bleeding time, but also exhibit thrombelastographic signs of hypercoagulability measured by shorter r- and k-times, increased α-angle and maximum amplitude compared to normal controls.[3] Interestingly, the latter study showed a significant negative correlation between haematocrit and signs of hypercoagulability. Moreover, isolated reduction of the haematocrit from 40 to 10% also resulted in thrombelastographic signs of hypercoagulability.[4] Reports of accelerated coagulation during haemodilution might therefore be influenced by changes in red cell sedimentation occurring with changing haematocrit. It is likely that this effect also depends on the physicochemical properties of the dilution fluid used and the time needed to process the coagulation measurements. Our *in vitro* and *in vivo* data on the influence of colloids and crystalloids on coagulation show an accelerated initiation of coagulation during moderate haemodilution with Ringer's lactate and gelatin for the slow-reacting intrinsic TEG measurements only.[5 6] In contrast to the data of Ng[1] and Ruttmann,[2] our results for accelerated coagulation were always accompanied by a reduction in clot firmness. Furthermore, we were surprised that, in the study by Ng and colleagues, the α-angle increased by about 71% in the haemodiluted group at 30 min, although platelets and fibrinogen decreased markedly. Given a normal value of 60°, this would mean that the angle would have reached values well above 90°. Was this really observed? Analysis of our *in vivo* data for the α-angle showed no significant difference in the intraoperative response profile (area under the curve minus baseline, $AUC_{A\text{-}D}$) of extrinsic TEG measurements between different fluid regimens (hydroxyethyl starch, modified gelatin 4% combined with a basal infusion of Ringer's lactate, or Ringer's lactate), and a significant difference in intrinsic TEG tracings between the two colloid groups only (Table 1).

Another question arises concerning measurements of concentrations of thrombin–antithrombin complexes (TAT). Why were concentrations of TAT much higher in the control group, and why did they also show a large standard deviation not observed in the haemodiluted group? Despite these inter-group discrepancies, the authors assumed that thrombin generation was increased in their haemodiluted patients as concentrations of TAT did not change during haemodilution, but showed an insignificant decrease in the controls.

A clinical study investigated coagulation after haemodilution with gelatin (in addition to a basal infusion of Ringer's lactate), which has also been associated with signs of hypercoagulability.[7] In this study, concentrations of TAT did not change significantly over several hours in haemodiluted or control patients Yet 3 h after surgery, a significant increase was observed, but only in control patients. Furthermore, all measurements of activated coagulation and fibrinolysis showed no differences between groups.

In summary, there is very little evidence that administration of i.v. fluids leads to clinically detectable hypercoagulability. Data from one study conducted in 1980, investigating only 30 'wet' and 30 'dry' patients during abdominal surgery without perioperative thrombosis prophylaxis, are insufficient to associate i.v. fluid therapy with development of deep venous thrombosis.[2 8] Some data indicate that the impairment of coagulation is the least when predominantly crystalloids are used.[5 6] These effects are seen as an advantage for surgical patients with respect to preventing further blood loss and limiting the need for transfusion of blood products. Moreover, reports on disseminated intravascular coagulopathy after administration of crystalloids are lacking in the literature. *In vivo*, the response of the coagulation system is mainly governed by the extrinsic pathway. Therefore, the impact of TEG measurements which are obtained without extrinsic activation, thus depending on the reactions provoked by contact to foreign surfaces, remains to be determined

Until it is proven clearly that hypercoagulability measured by TEG is not only an *in vitro* phenomenon but also relevant *in vivo*, it seems dangerous to recommend withholding i.v. fluids. Normovolaemia is essential for maintaining sufficient oxygen delivery to the tissues, and thus fluid therapy, not only influences coagulation, but also preserves organ function.

P Innerhofer
D. Fries
A. Klingler
W. Streif
Innsbruck, Austria

Editor—Thank you for the opportunity to reply to the letter by Dr Innerhofer and colleagues commenting on our paper.[1] We acknowledge Dr Innerhofer's point that the clinical significance of the hypercoagulability caused by crystalloid infusion remains to be evaluated. However, we believe that, given the prospective, randomized and controlled design, it is safe to state that our study is without the effect of any confounding variables.

We cannot agree with Dr Innerhofer that, because replacement with saline was 1:2, patients in the haemodiluted group in our study were hypovolaemic. The usual 25–30% retention rule is oversimplified and refers to an equilibrium state only The percentage retention of infused crystalloid in the intravascular compartment is dynamic. It depends upon the volume infused, the rate of infusion, and on when one is making the measurement. This has been discussed elegantly by Hahn and colleagues.[9] As we were allowing only 10 min for the infused fluid to distribute in our study procedure, 1:2 is the ratio administered to achieve normovolaemia. In fact, if we assume normovolaemia then the drop in haemoglobin (Hb) concentration after removal of 10, 20

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Table 1 Extrinsically- and intrinsically-activated TEG measurements during knee replacement surgery in groups randomized to receive hydroxyethyl starch 6% (HES) 200/0 5, modified gelatin 4% with Ringer's lactate (GEL), or lactated Ringer's solution (RL). Differences between groups were analysed by comparing the perioperative response profile (area under the curve, AUC_{A-D}) Data are median (interquartile range). A, baseline, B, before tourniquet release, C, end of surgery, D, 2 h later Statistically significant difference (AUC_{A-D} $P<0\ 05$). *GEL *vs* HES. No other statistically significant differences between HES, GEL and RL groups Analysis of repeated measures ANOVA (all groups pooled) showed no significant time effect

α-angle (°)	RL (*n*=20)	GEL (*n*=20)	HES (*n*=20)
Extrinsic TEG			
A	71 (64/76)	71 (66/72)	67 (64/71)
B	72 (66/74)	71 (63/72)	69 (64/73)
C	71 (66/77)	69 (62/71)	65 (60/69)
D	72 (61/76)	70 (66/73)	62 (58/67)
AUC_{A-D}	2 3 (–7.5/11 5)	–4 5 (–10 5/–0.5)	–5 8 (–17 3/2 8)
Intrinsic TEG			
A	71 (68/74)	68 (64/72)	70 (64/73)
B	69 (66/74)	70 (68/74)	67 (64/71)
C	71 (63/75)	69 (66/71)	67 (62/71)
D	67 (61/75)	70 (65/73)	66 (63/68)
AUC_{A-D}	2.5 (–11/7 5)	2 5 (–6/7 5)*	–9 3 (–12 5/–0.5)

and 30% of blood volume can be predicted by the exponential equations:[10]

$$Hb_{10\%}=Hb_0e^{-0\ 1}$$

$$Hb_{20\%}=Hb_0e^{-0\ 2}$$

$$Hb_{30\%}=Hb_0e^{-0\ 3}$$

where $Hb_{10\%,\ 20\%\ ,30\%}$ refers to the Hb concentration after removal of 10, 20 and 30% of blood volume and concomitant isovolaemic haemodilution. Hb_0 is the initial Hb concentration. In other words, the Hb concentration after removal of 10, 20 and 30% of blood volume should be 0.90 Hb_0, 0.82 Hb_0 and 0.74 Hb_0 respectively In our study, the values were 0.90, 0 80 and 0 74 respectively, which confirmed almost exact isovolaemia.

Dr Innerhofer's suggestion that the shortening of r- and k-times might be an artefact related to changes in red cell sedimentation is interesting, as they reported the effect may disappear when the TEG measurement was made more quickly. However, to accelerate measurement, the differences one would have to introduce are more than just the cell sedimentation rate. Certain components of the coagulation process would invariably be suppressed or enhanced The differences in TEG variables one observes may not be attributable to differences in measurement time alone The fact that an isolated reduction of haematocrit resulted in hypercoagulability[4] only proved that haemodilution-related hypercoagulability could develop in the absence of changes in concentrations of natural procoagulants or anticoagulants. It cannot be interpreted that the hypercoagulability is because of changes in red cell sedimentation during measurement, nor can the results exclude the possible contribution of changes in concentrations of natural procoagulants or anticoagulants.

We are surprised that Dr Innerhofer quoted the normal value of α as 60°, which, as far as we know, is usually quoted between 29 and 43° for *native* TEG.[11–13] In our study, the pre-dilution value of α was 26° in the haemodiluted group, increasing to 43° at 15 min, a 70% increase.

The higher mean and variance in the TAT concentrations of the control group were because of two patients with high TAT concentrations in this group. Thus, the two groups may not be comparable directly with respect to TAT concentrations and, therefore, this was not attempted What we have done is to follow the trend of TAT concentration in each group over time. Our suggestion that thrombin generation may be increased in the haemodiluted group was based on the lack of decline in TAT concentration despite haemodilution and a proportional decline in other haemostatic and cellular markers within this group

We fully agree with Dr Innerhofer that the native TEG is mainly measuring the contact activation (intrinsic) pathway of coagulation. Therefore the study, which demonstrated TEG features of hypercoagulability and yet prolonged bleeding time,[3] could not be simply discarded as reporting an artefact in the TEG measurement. The TEG is not a monitor of platelet function. Bleeding time measures adhesive properties of platelets (platelet–vWF–endothelium interaction) which is the major haemostatic defect observed in uraemic patients.[14] Although TEG variables are affected by thrombocytopenia, interestingly, the addition of platelets that are totally incapable of adhesion or aggregation improves the TEG, and the possible mechanisms for this have been reported [15]

Similarly, because TEG measures mainly the contact activation pathway, it is true that the clinical significance of our observation remains to be evaluated. We also agree that the patients we have studied probably had some pre-existing hypercoagulability. However, because of the parallel design of the study, this effect should be roughly similar in the haemodiluted and control groups Being aware of these limitations, and with our total agreement with Dr Innerhofer on the importance of adequate circulating volume, it has never been our intention to advocate withholding i.v. crystalloids from surgical patients. We shall need properly designed outcome studies to address this issue

K. F. J. Ng
C. C K Lam
L. C Chan
Hong Kong, China

1 Ng KFJ, Lam CCK, Chan LC *In vivo* effect of haemodilution with saline on coagulation. a randomized trial. *Br J Anaesth* 2002, **88**· 475–80
2 Ruttmann TG. Haemodilution enhances coagulation *Br J Anaesth* 2002; **88**. 470–2
3 Holloway DS, Vagher JP, Caprini JA, Simon NM, Mockros LF Thrombelastography of blood from subjects with chronic renal failure. *Thromb Res* 1987, **45**: 817–25
4 Iselin BM, William PFX, Seifert B, *et al* Isolated reduction of haematocrit does not compromise *in vitro* blood coagulation. *Br J Anaesth* 2001; **87** 246–9
5 Fries D, Innerhofer P, Klingler A, *et al*. The effect of the combined administration of colloids and lactated Ringer's solution on the coagulation system: an *in vitro* study using Thrombelastograph® Coagulation Analysis (ROTEG®) *Anesth Analg* 2002; **94**. 1280–7
6 Innerhofer P, Fries D, Margreiter J, *et al* Effects of perioperatively administered colloids and crystalloids on primary platelet-mediated hemostasis and clot formation *Anesth Analg* 2002; **95**: 858–65
7 Hoblsch-Hagen P, Wirleitner B, Mair J, *et al* Consequences of acute normovolaemic haemodilution on haemostasis during major orthopaedic surgery. *Br J Anaesth* 1999, **82** 503–9
8 Janvrin SB, Davies G, Greenhalgh RM. Postoperative deep vein thrombosis caused by intravenous fluids during surgery *Br J Surg* 1980, **67**. 690–3
9 Hahn RG, Drobin D, Stahle L Volume kinetics of Ringer's solution in female volunteers. *Br J Anaesth* 1997, **78**. 144–8

10 Brecher ME, Rosenfeld M. Mathematical and computer modeling of acute normovolemic hemodilution. *Transfusion* 1994; **34**: 176–9

11 Haemoscope Corporation. Thrombelastograph coagulation analyzer. Operational Manual 43; 1990. Skokie, IL, USA

12 Miller BE, Bailey JM, Mancuso TJ, *et al.* Functional maturity of the coagulation system in children: an evaluation using thrombelastography. *Anesth Analg* 1997, **84**: 745–8

13 Caprini JA, Zuckerman L, Cohen E, *et al* Comparison of thromboelastography with common coagulation tests. *Thromb Haemost* 1981, **46**: 362

14 Weigert AL, Schafer AI. Uremic bleeding: pathogenesis and therapy. *Am J Med Sci* 1998; **316**: 94–104

15 McNulty SE, Sasso P, Vesci J, Schieren H. Platelet concentrate effects on thromboelastography. *J Cardiothorac Vasc Anesth* 1997, **11**. 828–30

Quality of pre-hospital emergency ventilation in patients with severe head injury

Editor—We would like to comment on the article by Helm and colleagues,[1] in which two specific outcomes of out-of-hospital ventilation, oxygenation and ventilation are investigated. The article concluded that tracheal intubation and controlled ventilation in the pre-hospital setting do not guarantee optimal oxygenation or ventilation. Optimal oxygenation was achieved in 85.2% of patients. In 1996, Stocchetti and Furlan[2] demonstrated that 57% of patients with head trauma had an arterial oxygen saturation <90% at the scene of the accident. If this patient group is similar, the system that Helm and colleagues describe provides excellent improvement in the on-scene oxygenation of head-injured patients, especially as some of the poorly oxygenated patients had significant chest injuries and might well have been difficult to oxygenate, even in the hospital intensive care setting. With regard to 'adequate ventilation', we accept that, while capnography can be difficult to interpret in the hypovolaemic patient or those with severe lung contusion, it still provides invaluable information. In addition to providing evidence of appropriate ventilation, capnography also provides confirmation of tracheal intubation and detection of disconnection. Both the Intensive Care Society,[3] and the Association of Anaesthetists,[4] have produced guidelines for transfer of the critically ill. Both organizations advise the use of capnography. We see no reason why primary transfers of the critically ill should have lower standards than secondary transfers, particularly in doctor-led systems. Lastly, the authors comment that blood gas analysis is the gold standard in ventilatory monitoring, but is impractical in the pre-hospital setting This is usually the case, but with the advent of hand-held devices that can perform blood gas analysis as well as other blood tests, it may be that in the few patients with prolonged scene times or long transfers, this level of monitoring may become practical.

M J. Richards
D. J. Lockey
Bristol, UK

Editor—First of all, we would like to thank Drs Richards and Lockey for their comments on our article.[1] We agree totally with their recommendations and have followed them on a routine basis in our emergency medical service in Ulm, Germany for 3 yr.

With regard to 'adequate ventilation', capnography can be difficult to interpret in the hypovolaemic trauma patient or those with severe lung contusion.[5,6] The use of capnography for controlling artificial ventilation is therefore limited in this group of trauma patients. However, we agree that capnography provides confirmation of tracheal intubation and detection of disconnection, and that its routine use should be recommended as a monitor of safety in ventilated patients in the pre-hospital setting. Capnography has been mandatory in any ventilated patient received into our emergency medical service for nearly 3 yr.

Blood gas analysis is the gold standard in ventilatory monitoring. In the pre-hospital setting, especially in primary rescue missions of traumatized patients, it seems to be impractical as a monitoring method on a routine basis because it is invasive, time-consuming and non-continuous. Again we agree with Drs Richards and Lockey when they recommend blood gas analysis in the few cases with prolonged scene times or long transfers. We have been performing blood gas analysis, as well as determination of haematocrit and plasma electrolytes, in such cases using a hand-held blood gas analyser (i-Stat; Hewlett Packard) on a routine basis for more than 2 yr.

M. Helm
Ulm, Germany

1 Helm M, Hauke J, Lampl L. A prospective study of the quality of pre-hospital emergency ventilation in patients with severe head injury. *Br J Anaesth* 2002; **88**: 345–9

2 Stocchetti N, Furlan A, Volta F. Hypoxaemia and arterial hypotension at the accident scene in head injury. *J Trauma* 1996; **40**: 764–7

3 Intensive Care Society. *Guidelines for Transport of the Critically Ill Adult* Intensive Care Society, 1997

4 Association of Anaesthesists. *Recommendations for the Transfer of Patients with Acute Head Injuries to Neurosurgical Units.* Association of Anaesthesists, 1996

5 Morley AP Pre-hospital monitoring of trauma patients: experience of an emergency helicopter medical service. *Br J Anaesth* 1996; **76**: 726–30

6 Helm M, Hauke J, Lampl L, Sauermuller G, Bock KH. Arterial to end-tidal carbon dioxide gradient and Horovitz-quotient—of value in diagnosing blunt chest trauma? *Br J Anaesth* 1995; **74**: 127

Mechanical closure of the vocal cords with the LMA ProSeal™

Editor—I was interested to read the case report by Brimacombe and colleagues[1] listing the features of the LMA[†] ProSeal™ together with the insertion problems ascribed to its bulky nature. The recently introduced Airway Management Device (AMD™) was designed to address the same shortcomings associated with the LMA Classic™, whilst allowing easy and less traumatic insertion.[2,3]

The mechanical closure described by Brimacombe is explained in detail,[1] and corroborates a similar phenomenon seen when using a pre-production prototype in an early stage of the development of the AMD™. Before the development of the 'arrow-head shape' of the currently available device, the anteroposterior diameter of the inflated lower cuff with its unique central drainage channel was some 50% greater. Over-enthusiastic insertion and inflation of this cuff beyond its optimal position resulted in near complete airway obstruction, presumably of similar aetiology (i.e. forward displacement of the glottic inlet). As stated, the application of cricoid pressure with the classic LMA simulates the same conditions.[4]

The less bulky nature of the AMD™ should not cause such compression opposite the glottic inlet. The slim anteroposterior profile of the lower cuff, when inflated before insertion, greatly reduces the risk of inadvertent intrusion beyond the oesophageal sphincter. The upper cuff, designed to elevate the tongue and lift the epiglottis clear of the laryngeal inlet, in a fashion similar to laryngoscopy, ensures an unobstructed airway whilst maintaining access to the oesophagus.

[†] LMA® is the property of Intavent Limited.

M. J. O'Neil
Huddersfield, UK

Editor—We would like to thank Dr O'Neil for confirming our observation of mechanical cord closure.[1] It would seem that this is a potential problem with any extraglottic airway device forming a seal in the hypopharynx, and as such is also likely to occur with the Laryngeal Tube Airway™[5] and Pharyngeal Airway Express™[6] devices, which are very similar to the Airway Management Device or AMD™. However, we feel it is somewhat premature for Dr O'Neil to claim, on design grounds alone, that the AMD™ cannot cause mechanical cord closure and yet form an effective seal with the hypopharynx. In its resting state the hypopharynx is usually closed (as readily observed during gastroscopy). Any device occupying the hypopharynx sufficiently to form a seal must open it and push the glottis anteriorly. In a percentage of patients with unfavourable anatomy, this will inevitably cause glottic compression. In our original report, we stated that the incidence of mechanical cord closure with the ProSeal™ was 0.4% (4/915).[1] Our latest figure from ongoing data collection is 0.3% (19/6321). We consider that the incidence of mechanical cord closure for the Laryngeal Tube Airway™, Pharyngeal Airway Express™ and AMD™ will be similar once sufficient data has been collected.

J. Brimacombe[1]
C. Richardson[1]
C. Keller[2]
S. Donald[1]
[1]*Cairns, Australia*
[2]*Innsbruck, Austria*

1 Brimacombe J, Richardson C, Keller C, Donald S. Mechanical closure of the vocal cords with the ProSeal™ laryngeal mask airway. *Br J Anaesth* 2002; **88**: 296–7

2 O'Neil MJ. Development and evaluation of the AMD™ including comparison with LMA in spontaneously breathing anaesthetized patients. *Today's Anaesthesist* 2001; **16**: 98–103

3 Cook TM, Gupta K, Gabbott DA, Nolan JP An evaluation of the airway management device. *Anaesthesia* 2001; **56**: 1–6

4 Brimacombe J, Berry A. Mechanical airway obstruction following cricoid pressure with the laryngeal mask airway. *Anesth Analg* 2001; **78**: 604–5

5 Brimacombe J, Keller C, Brimacombe L. A comparison of the laryngeal mask airway ProSeal™ and the laryngeal tube airway in paralyzed anesthetized adult patients undergoing pressure-controlled ventilation. *Anesth Analg* 2002; **95**: 770–6

6 Voyagis GS, Iatrou C, Dimitriou V. Safety of the new pharyngeal airway (PAXexpress) as a ventilatory device. Preliminary data. *Eur J Anaesthesiol* 2002; **19**: A143

Management of failed intubation in a septic parturient

Editor—I was dismayed to read the case report from Hinchliffe and Norris[1] 'Management of failed intubation in a septic parturient', which actually presents an example of how to *not* manage a difficult obstetric case! In the first instance, trainees were left to, or decided to, take on a high-risk case without consultant support. Surely we have learned, from the Confidential Enquiries into Maternal Deaths,[2] that most deaths in obstetrics associated with anaesthesia involve less experienced anaesthetists providing emergency anaesthesia for Caesarean section. When a consultant arrived, however, the management decision was puzzling. In a patient in whom it had been decided that laryngoscopy and intubation were either extremely difficult or even impossible, it was elected to proceed to epidural anaesthesia. What would have been done in the event of an accidental total spinal anaesthetic? In this particular case, the decision to proceed to epidural anaesthesia was taken despite the fact that the patient was only just managing to maintain adequate arterial oxygen saturation breathing oxygen 100%, and was confused and haemodynamically unstable!

This patient should have undergone awake fibreoptic intubation from the start. Anything less borders on negligence. Muddled thinking, as illustrated in this case report, is exactly what leads to disasters.

M. O'Leary
NSW, Australia

Editor—I read with interest the case report by Hinchcliffe and Norris.[1] I have serious concerns about the way this patient was managed. The patient, a young, obese (105 kg) nurse, was very unwell on admission and the fetus was in considerable distress. A decision to proceed to Caesarean section was made. Assessment of the patient found her to have a Mallampati score of 3 and a 'cricothyroid membrane that was difficult to identify'. No reason is given for the difficulty in identification. I assume she had a short fat neck, in keeping with her weight. These factors, in combination with her obesity, indicate there is a substantial risk for her being a difficult intubation, in a population where the risk is only 1 in 300. Nevertheless, the decision to proceed with general anaesthesia was taken, without discussing the case with the consultant obstetric anaesthetist. Surely such a complex case with numerous risk factors demands consultant input at an early stage? Moreover, after induction of anaesthesia, she was given an inadequate dose of succinylcholine (100 mg); a dose of 150 or 200 mg would have been appropriate. I wonder whether incomplete muscle relaxation contributed to the poor view at laryngoscopy? Having anaesthetized and paralysed the patient, why was no attempt made to pass a gum elastic bougie on visualization of the epiglottis? Surely one attempt was warranted.

The other major concern I have is, had you been unable to ventilate the patient after induction, the option for formation of an emergency surgical airway was severely limited because of poor landmarks. I suggest that the decision to proceed with general anaesthesia in someone with serious potential airway problems was inappropriate. The appropriate course of action would have been to perform a regional technique (epidural), or an awake fibreoptic intubation at the outset. Although systemic infection is a relative contraindication to regional techniques, Chestnut[3] found only one case of epidural infection in 500 000 obstetric epidurals, with an assumed incidence of 1% bacteraemia. If we assume this episode of epidural infection occurred in one of those patients who was bacteraemic, this indicates a risk of 1 in 5000 for developing epidural infection in such patients compared with a risk of less than 1 in 300 for a serious airway problem on induction of general anaesthesia in the obstetric population. Of the 531 patients in the study by Goodman and colleagues,[4] none developed epidural or spinal infection despite having a regional technique in the presence of chorioamnionitis. Although there is a theoretical risk for seeding infection in the epidural/spinal spaces in those who are bacteraemic, hard evidence appears to be lacking in patients having 'single shot' regional techniques. The risk benefit ratio in this case appears to favour a regional technique.

The reasons given for not performing an awake fibreoptic intubation are, at best, dubious. We must remember that what we should do is take the safest option, in the patient's best interest. It is worth drawing attention to a recent editorial in The Royal College of Anaesthetists Bulletin,[5] which claims that there have been three deaths attributable to failed intubation by trainee anaesthetists in pregnant patients, since the last triennial report into maternal deaths (1997–1999)[6] was published. It is better to take a little longer over a procedure and inflict some discomfort if this is the safest option, rather than rush into something potentially disastrous.

M. F. Dunsire
London, UK

Editor—Thank you for the opportunity to reply. Dr O'Leary appears to misunderstand the role of case reports of this type, which is partly for interest, and partly to illustrate some wider lesson. The lesson in our case is that regional anaesthesia may remain the obstetric anaesthetist's best option, even when systemic infection is present (albeit after antibiotic treatment). Dr Dunsire makes a similar point. Our description of events does not pretend to be an essay on how to manage such cases.

The suggestion that the case was mismanaged because of lack of experience on the part of the senior trainees involved is misplaced. The specialist registrars both possessed the FRCA, in addition to several years experience of obstetric anaesthesia. Only in the UK and Eire would such doctors still be part of a training scheme, and this is reflected in the nature of their clinical responsibilities. The decision to request additional assistance from a colleague with particular experience or skills reflects sound clinical practice not lack of competence.

In contrast to Dr O'Leary's remarks, the management of this case enshrines many of the principles contained in maternal mortality and CEPOD reports;[2 6] a formal assessment of the airway was made, assistance was requested, preparations for difficult intubation were made, a failed intubation drill was adopted promptly without repeated attempts, and intensive care was involved early

Both correspondents suggest that awake fibreoptic intubation should have been performed from the outset. Indeed, Dr O'Leary says not to do so verges on negligence. We disagree. We acknowledged in our report that awake intubation might have been the best option, but there is no consensus on when this is indicated on the basis of predictive factors, and the problems with this approach have been summarized by Yentis.[7] Even when awake intubation appears to be indicated, a cooperative patient is still required. Is a woman with a fever in advanced labour with fetal distress likely to be cooperative? The ASA difficult airway guidelines[8] suggest regional anaesthesia (as in our case) or fibreoptic intubation under anaesthesia as options in this context.

Even if the indications for awake intubation were clear, which they are not, it is futile to argue, as a current standard of practice, that all potentially difficult cases undergo awake intubation, when the reality (at least in the UK) is that most anaesthetists lack the necessary skills, training and equipment, especially for a case like this.[9] Difficult cases require knowledgeable, skilled doctors to exercise their clinical judgement, not the reflex application of a single 'solution'.

A. M. Norris
D. Hinchliffe
Nottingham, UK

1 Hinchliffe D, Norris A. Management of failed intubation in a septic parturient *Br J Anaesth* 2002; **89**. 328–30
2 Report on Confidential Enquiries into Maternal Deaths in the United Kingdom 1985–1987 London: HMSO, 1990
3 Chestnut DH. Spinal anaesthesia in the febrile patient *Anesthesiology* 1992; **76**: 667–9
4 Goodman EJ, Dehorta E, Taguiam JM. Safety of spinal and epidural anaesthesia in parturients with chorioamnionitis. *Reg Anesth* 1996; **21**: 436–41
5 The Royal College of Anaesthesists. Bulletin 14; July 2002. 662–3
6 Why Mothers Die. Report on Confidential Enquiries into maternal deaths in the United Kingdom 1997–1999. London: RCOG Press, 2001
7 Yentis SM. Predicting difficult intubation–worthwhile exercise or pointless ritual? *Anaesthesia* 2002; **57**: 105–9
8 American Society of Anesthesiologists. Practice Guidelines for management of the difficult airway: A report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. *Anesthesiology* 1993; **78**: 597–602
9 Popat MT, Srivastava M, Russell R Awake fibreoptic intubation skills in obstetric patients: a survey of anaesthetists in the Oxford region. *IJOA* 2000; **9**: 78–82

Survival and success of weaning from prolonged ventilation

Editor—I was interested in the abstracts from the Lane Fox Respiratory Unit regarding their results in weaning and survival after prolonged ventilation.[1 2] Following the recent NHS Modernisation Agency Report 'Weaning and long-term ventilation',[3] the experiences of units like Lane Fox will become increasingly important.

Unfortunately, there are some problems with both the tables in the abstracts that make them difficult to understand. The first abstract stated that the total number of patients admitted was 153, of which 53 survived and 42 died (Table 17).[1] What happened to the other 58? From the table in the subsequent abstract, it appears there were 111 survivors, so perhaps the 53 in Table 17 were the patients who were ventilator-dependent on discharge[2] Of the survivors, Table 17 *appears* to state 35% were ventilator-dependent on discharge, whereas the text states 'Of the survivors about one-half were ventilator-dependent at hospital discharge'. Thus the '35%' in the table presumably refers to the percentage of ventilator-dependent patients at discharge compared with the total number of patients admitted (53/153), with 53 of the 111 survivors being ventilator-dependent (48%). The text refers to ventilator dependency at discharge as 21/94 (22%) for 'in house ICU' and 32/59 (54%) for 'outside ICU', but the denominators are the total numbers in each group admitted to the unit, not the total number of survivors at discharge, which would have been more meaningful in this context.

The second abstract is difficult to disentangle, mainly due to the inadequate and misleading row labelling of the table (Table 18).[2] There is essentially a repetition of the same information in rows two and four. Row two, labelled 'All survivors (% of total patients)', refers to all survivors to hospital discharge (% of all admissions). The final row four labelled 'Dead (% of total patients)' is the number who died in hospital (% of all admissions), which is the same information as row two. However, the table omits the pertinent information about those who died between hospital discharge and 2 yr. Once you have worked out that row four does not give this information, you must start searching for it—some of it is in the text of this abstract, and some in the text of the previous abstract. The number of deaths

Table 1 Variables recorded from the Lane Fox Unit for weaning from mechanical ventilation

		All patients	**Survivors**	**Dead**	***P*-value**
Number (%)		153	111 (73%) 53 (35%) ventilator-dependant at discharge	42 (27%)	
Age	Median	63	61	71	<0.05
	Interquartile range	49–72	46–67	61–76	
Days in referring ICU	Median	20	14	31	<0.05
	Interquartile range	8–39	7–34	17–58	
APACHE II (ICU Admission)	Median	15	14	16	>0.05
Predicted mortality	Median	16.5%	16%	19%	>0.05
TISS	Median	426	373	541	>0.05
Cost per stay on LFU	Median	£22 035	£20 066	£26 609	>0.05

ICU=intensive care unit; LFU=Lane Fox Unit.

between live hospital discharge and 2 yr appears to be a further 35 patients, derived from the admission to 2 yr survival of 50%, giving a post-live-discharge to 2 yr survival of 68%. This can be calculated to have included six deaths in the neuromuscular/chest wall group (post-live-discharge to 2 yr survival of 85%), 14 deaths in the COPD group (post-live-discharge to 2 yr survival quoted at 52%), and three deaths in the postoperative group (post-live-discharge to 2 yr survival of 82%). The text is less than helpful in stating 'postoperative patients had the highest mortality, neuromuscular/chest wall the lowest'[2] without making it clear this was in-hospital mortality. Additionally, it would have been interesting to know how many of those weaned at discharge remained off the ventilator at 2 yr.

While I appreciate abstracts must be concise, I found these interesting and important abstracts confusing, mainly because of the tables.

A. C. David
Essex, UK

Editor—We thank Dr David for her comments and are pleased that our abstracts were considered important. We apologize, however, that there was difficulty understanding the texts.

With reference to the first abstract,[1] entitled 'Outcomes, cost and long-term survival of patients referred to regional centre for weaning from mechanical ventilation', the table has unfortunately been misprinted in the journal. The original table listed the number of survivors as 111, 53 of whom were using a ventilator at discharge from hospital. Thus, the overall percentage of patients who required ventilatory assistance at discharge was 35% (53/153) and over half of the survivors (58/111=52%) were free from any form of support at discharge. The text was written to emphasize this point. Unfortunately, the interquartile ranges have also been inaccurately reproduced. We have included a corrected table above (Table 1).

At our presentation to the ICS 'State of the Art' meeting, a comparison of patients referred from outside ICUs with those referred from the in-house ICU was made. Only a limited amount of information can be included in the abstract. Expressing the denominators as the total number admitted to the unit would not, however, have been meaningful.

With reference to the second abstract,[2] 'The influence of diagnosis on survival and success in weaning patients from prolonged mechanical ventilation', rows two and four of the table contain essentially the same information as it was thought this would help the reading of the abstract. In the original, the table was placed before the text and was intended to summarise the outcomes at hospital discharge. However, the long-term mortality data had to be abbreviated for the abstract. It was included as text because combining this information with the previous data on outcomes at hospital discharge would have added to the complexity of the table. In addition, follow-up data on those who remained ventilator-free at discharge were incomplete when the abstract was submitted. We agree that this is important.

We hope our comments answer Dr David's concerns. Fuller data from our unit are being written up and we hope that they will be of interest when published.

D. V. Pilcher
A. C. Davidson
London, UK

1 Pilcher DV, Hamid S, Williams AJ, Davidson AC. Outcomes, cost, and long-term survival of patients referred to regional centre for weaning from mechanical ventilation. *Br J Anaesth* 2002, **89**. 361P

2 Pilcher DV, Hamid S, Williams AJ, Davidson AC. The influence of diagnosis on survival and success in weaning patients from prolonged mechanical ventilation. *Br J Anaesth* 2002, **89**: 362P

3 Critical Care Programme Report. *Weaning and Long-term Ventilation*. NHS Modernisation Agency, April 2002

British Journal of Anaesthesia **89** (6): 940–4 (2002)

Book Reviews

The Electronic Anesthesiology Library (TEAL) on CD-ROM (Volume 7: 1997–2001). Published by Lippincott, Williams and Wilkins, Philadelphia. ISBN 0-7817-3616-1.

This is the latest TEAL CD of a series that has become established as a key resource within active anaesthetic departments. This is a review of the latest 5-yr CD version, although there is, allegedly, a 10-yr DVD version as well. The contents and access are familiar to anyone who has used the previous volumes of the CD. There do not appear to be any major changes in the software, which uses a Windows and Mac compatible format and allows several ways of searching the database of journal content. As with all educational material, it has both good and bad points.

Its main advantage over internet accessible library or search facilities is the ability to access complete papers (of *Anesthesiology*, the *British Journal of Anaesthesia*, *Anesthesia and Analgesia*, and the *Canadian Journal of Anaesthesia*) rather than the more ubiquitous Medline format of a title and abstract. The ability to print and save entire papers or just appropriate graphs to illustrate a lecture or presentation is one of the strongest points of this package.

The 'Knowledge Finder' software is easy to install if you have not used it before, and is almost intuitive enough to begin searching the 5-yr database. There is a handbook in the front of the jewel case, which contains enough information to make the most of the search tools. Sadly, there is no way to copy the software and the databases onto a computer without having the CD in place. Previous reviews[1–3] have mentioned the variety of search strategies available. There is an option to simply review the tables of contents of the journals, but whilst this is effective, it is little better than using the bound paper versions. The other two search methods are more rapid—one uses a 'fuzzy logic' to match free text to appropriate papers, the other uses the more familiar dictionary approach with, for instance, keywords or authors.

The results are displayed as a page of summaries. The information is concise and is ranked according to the nearest match to the search strategy The matching appears to be prioritized to the nearest text match and then in reverse chronological order. This sometimes makes apparently very similar papers appear out of sequence. To move from the summaries page to view the complete papers is achieved by double clicking or hitting a button with two eyes and no explanation! The page with the complete paper can also display a thumbnail area with all the illustrations, graphs and tables from the paper. This is a very valuable tool; it is of great use when the need is to find that particular graph that explains the concept so well for a presentation. Finding it (requiring moving through the windows toolbar and finding the figures-tables window) is worth the effort.

The page with the complete paper on has a few more interesting features. The cursor becomes a hand once over the text, but unlike other programs it does not scroll the text, it highlights the text for editing. Even this is a little tricky because it often misses the parts you want. There are several buttons with no explanation that with some simple experimentation appear to increase or decrease the line spacing—why?

Moving between the selected papers can be achieved by using the next/previous buttons. They can also be selected using the left and right buttons, but using the up/down ones moves to the next reference in the database. This is a little disconcerting the first time it happens, and just irritating after that.

The final irritation is the inability to copy the key elements of the reference into any of the 'reference' software packages. Surely the majority of purchasers of this CD will intend to use the results of their searches in one literary form or another—be it a review article, the discussion section of a paper, or even a PowerPoint slide presentation.

What do I really think about this CD? It remains a very valuable resource for a department, and is useful for individuals who need to both search for and read complete papers. It is this that allows it to stand against the internet search systems. I certainly would not be without this volume or the previous ones. However, the costs involved in buying the CD are high, and the inability to copy it to one's 'working' laptop is a significant problem. It is high time the software was updated.

Would I recommend that you buy it? Yes. I would recommend that your department has one, and that it is under lock and key. The inability to load a working copy on at least one machine is a major risk when the CD is 'lost'. The 5-yr database is complete and, unless you lose a copy, it would make sense to get a new CD every 5 yr.

C. Dodds
Middlesbrough, UK

1 Prys-Roberts C. *The Electronic Anesthesiology Library (TEAL) on CD-ROM* (Volume 3: 1993–1997). *Br J Anaesth* 1999; **82**: 155–6
2 Kenny GNC. CD Review: *The Electronic Anesthesiology Library 1996–2000 TEAL CD-ROM*. *Br J Anaesth* 2001; **87**: 944
3 Parsons D. *T.E.A.L. The Electronic Anesthesiology Library on CD-ROM, 1991–1995*. *Can J Anesth* 1997; **44**: 341

Fundamental Principles and Practice of Anaesthesia. P. Hutton, G. M. Cooper, F. M. James III, J. F. Butterworth IV (editors). Published by Martin Dunitz, London. Pp. 1072; indexed; illustrated. Price £95.00. ISBN 1-899066-57-8.

This is a major textbook primarily aimed at the trainee anaesthetist, and covers core knowledge in anaesthesia. The book is divided into sections, approaching the material from three aspects. The first section is 'Basic Anaesthetic Practice'. This covers the process of giving anaesthesia for surgery, and management of the normal patient perioperatively and post-operatively. It also provides a basic outline of intensive care medicine. The second section is entitled 'Integrated Basic Sciences' and covers biochemistry, physiology, pharmacology, and physics with clinical measurement. A third section 'The Presenting Patient', covers the clinical assessment and management of various categories of patient undergoing anaesthesia, who could potentially cause problems. Finally, a miscellaneous section, 'Special Subjects: Physiology and Pharmacology' presents theoretical or practical topics, which do not fit readily into the other sections.

The book is edited from both sides of the Atlantic, but the majority of the contributors are from the UK and the book has a definite English, rather than transatlantic 'flavour'. It is, however, designed to provide the basic knowledge suitable for anaesthesia postgraduate examinations across the world, including those held in the UK, Ireland, USA, Canada, Hong Kong, and Australasia.

Initial impressions are of a book of just over a thousand pages, covering every topic that trainees and indeed established

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

specialists, might wish to look up. Topics are approached from both the practical and theoretical points of view. Text, tables and diagrams are clearly presented and well laid out In spite of multiple contributors, there is a notable uniformity throughout the text, which pays tribute to the editing. The text is well organized, clearly written and with a minimum of opinion, hypothesis and references. It presents the basics of each topic without ambiguity, and includes some references at the end of each chapter, for further reading where required. The compactness of the format often belies the information content, which can be very concentrated.

The book is extremely well supported with photographs (both colour and black and white), line diagrams and tables, all of which are of a high quality Background colouring to highlight the line diagrams and tables is in various tones of purple, which certainly make the diagrams stand out, in fact strikingly so! However the reader's eyes soon become accustomed to this effect. Splits of diagrams from the relevant text are inevitable in all text books, and will obviously increase with large numbers of diagrams and photographs *Fundamental Principles and Practice* is exceptionally well illustrated, but the reader sometimes pays the price with increased page turning to view the diagrams or tables referred to. Personally, I found some of the labelling in the diagrams a little too fine for easy reading. Photographs, although compact, are of excellent quality and illustrate the accompanying text well; even the x-rays and CT scans making their point clearly.

'Basic Anaesthetic Practice' effectively constitutes a manual of good practice for the anaesthetic trainee, starting with basic decision-making and working through the process of giving an anaesthetic for surgery. Excellent chapters are given on post-operative care and airway management. The text is always centred around good anaesthetic practice, but is not prescriptive and avoids the pitfalls of becoming too didactic or providing 'anaesthetic recipes'. Although the authors do not hesitate to delve into the detailed underlying anatomy or physiology where appropriate, the discussion never becomes so esoteric that the reader loses sight of the practical clinical implications.

The chapter on high-dependency and intensive care is only 23 pages long, but manages to highlight all of the main issues of clinical importance very competently. Within these pages the authors manage to cover scoring systems not only for patient severity, but also for sedation, liver failure, and acute lung injury. Different organ system failures are discussed, with a brief but clear presentation of underlying pathophysiology, and a basic rationale for management. Even sections outlining the primary issues in ethics, death and dying, and communication in intensive care, are included. These few pages will be an invaluable aid to new trainees fresh to intensive care medicine This first section presents the principles of sound clinical practice, underpinned with detailed basic sciences where appropriate, and is highly successful.

'Integrated Basic Sciences' takes a novel approach to biochemistry, physiology and pharmacology, which are traditionally presented as separate disciplines. The emphasis is laid on integration of the basic sciences within each topic. Topics are approached by trying to present a seamless discussion, moving from the atomic/molecular level through to tissue/organ level, with relevant pharmacology woven into the account.

Thus the opening chapter in this section spans basic physical chemistry, biochemistry, intermediate metabolism, cell division, and genetics. This is challenging coverage for the reader as the material is concentrated into 30 pages Depth of discussion in not necessarily sacrificed in the interests of covering ground, and this is not easy reading. However, the overview provided gives the various components, which are usually covered individually, a new perspective seen within the background context of the cell.

In the 'Cardiovascular Physiology and Pharmacology' chapter, physiology and pharmacology mesh together naturally. The consideration of anti-arrhythmic drugs and inotropes fit well into the overall scheme. The reader really does get an impression that the whole is greater than the sum of its separate parts Similarly, in discussion of renal physiology, the inclusion of pharmacological implications adds an extra dimension. However, in the chapter on liver biochemistry and physiology, although a very good discussion of drug metabolism is presented, the drug regimens often applied to liver failure patients are not mentioned.

In general, this integrated approach to biochemistry, physiology and pharmacology is very successful, adding an extra dimension to the reader's understanding. The result is analogous to the difference between Grant's regional approach to anatomy *vs* Gray's systemic approach Sometimes an understanding of the regional anatomy is more useful in practice than an understanding of the separate systems of nerves, muscles and bones.

In contrast, the physics, clinical measurement and statistics are presented as separate sections These chapters are well presented with good coverage of all topics. A thorough section on clinical measurement and safety, together with a clear but concise section on statistics completes what is a very commendable basic sciences package.

'The Presenting Patient' is a section reminding readers of their roots as medical practitioners. It outlines the anaesthetic implications of various common disease states, which potentially cause problems in patients presenting for anaesthesia This is effectively a handbook for practising anaesthetists who are likely to be faced with such patients. Excellent summaries and guidelines are provided for the assessment and management of common presentations, including such conditions as ischaemic heart disease, diabetes mellitus, renal failure, hepatic failure, obesity, and many more. These are all problems that trainees (and indeed all anaesthetists) are more than likely to encounter in everyday practice. The section is well written, concise, and based on good clinical practice

'Special Subjects' has a wealth of topics in it, ranging from accounts of how to perform procedures such as insertion of jugular CVP lines, to more topical material such as a brief account of cell adhesion molecules. This section, apart from providing a home for miscellaneous topics, will also enable the volume to 'keep up to date' against the ever-changing background of medical fashion

Here is a book which has multiple roles It provides the new trainee with a basic introduction to anaesthetic practice and the role of the anaesthetist. It is also a textbook of basic sciences written from the anaesthetic point of view by practising anaesthetists, to provide core knowledge for postgraduate examinations and further learning. 'The Presenting Patient' section is a valuable guide and *aide memoire* for the assessment of patients and the management of common clinical problems that arise in everyday anaesthetic practice It is a book that sets out to be all things to all anaesthetists in training, not only for our own trainees in the UK and Ireland, but throughout the English-speaking world.

The difficulties facing such a project are substantial. It has to obtain the right spectrum and depth of coverage, presenting complex basic sciences in a clear, organized fashion, but in a way relevant to anaesthesia. It should provide clear uncluttered guidelines in clinical matters without becoming over prescriptive, and yet encourage trainees to develop their clinical skills using basic sciences, thus avoiding clinical practice based on mindless algorithms.

I believe the editors have achieved these ambitions and produced an admirable foundation text The volume is inevitably substantial and the concentration of material is sometimes daunting, but it truly is a resource containing the basics of our speciality. I would have no hesitation in recommending this book to trainees and senior colleagues alike. It contains all you need and more to become and remain a 'proper' anaesthetist! I have no doubt that successive editions will go from strength to strength.

E. S. Lin
Leicester, UK

Clinical Data Interpretation in Anaesthesia and Intensive Care. S. Bonner and C. Dodds (editors). Published by Churchill Livingstone, London. Pp. 278; indexed; illustrated. Price £24.99. ISBN 0-443-06453-9.

This book is a gem! Its aim is succinctly articulated in its Preface. 'This book grew out of a desire to provide ongoing CPD in clinical data interpretation for both consultants as well as trainees, together with an insight into some newer methods of investigations, of relevance to anaesthesia.'

It succeeds in this aim admirably. A large amount of information has been packed into a small book and yet the content remains accessible and relevant. The book is multi-author, each of the nine chapters having contributions from between one and four authors. The book covers a number of areas relevant to clinical practice in anaesthesia: respiratory disease, cardiology, neurosurgery, orthopaedics and trauma, general anaesthesia, intensive care medicine, obstetric anaesthesia, paediatric anaesthesia, and pain management. Each chapter begins with a short introduction to the tests on which the data is to be presented. These introductory sections are clear and useful and in one or two cases the authors seem to manage to describe clearly and usefully, in three or four pages, material which is frequently described in textbooks at much greater length with considerably less clarity. The descriptions of thrombelastography and blood gas analysis are cases in point. There follows a series of short questions on data interpretation, usually 25–30 in number, although there are only 10 on obstetric anaesthesia and 10 on pain management The questions are short, usually occupying about half a page, and consist of a clinical scenario together with relevant clinical data such as a chest x-ray, ECG, set of blood gas results, or a cardiotocograph (CTG). The final section of each chapter consists of the answers to the preceding questions plus explanations that are sufficient without being overwhelming. References for further reading are given.

The book has a few minor weaknesses. The obstetric section seems short, having only 10 questions, six of which are on the CTG. The pain management section focuses solely on chronic pain and, again, contains only 10 questions. The x-rays that are reproduced in many of the questions have frequently lost detail in being reduced to fit into the book. However, with regard to this last issue, the authors and publishers presumably had to tread a line between producing a large expensive book full of high resolution images, and a smaller book with perhaps slightly less clear images at a reasonable price. I feel that they have made the right choice.

This is a book that will fit easily into a briefcase. One can dip into it in those short gaps that appear in the working day that can be long enough to be tedious but too short to retire to the office or the library. It will be useful to trainees preparing for the final fellowship examination. (The SpRs to whom I showed it all seemed to feel that it was an excellent little book.) It will also certainly be useful to consultants seeking digestible CPD material who wish to supplement their reading of the literature, particularly review articles, with material that has a strong clinical flavour. This book is packed with useful knowledge, but its great virtue is the elegance with which it places the application of that knowledge into context.

S. J. Howell
Leeds, UK

Problems in Anesthesia Series. L. A. Fleisher and D. S. Prough (editors-in-chief). *Quality, Safety, Risk and Outcomes.* L. Fleisher and D. Prough (editors).. Published by Lippincott, Williams and Wilkins, Hagerstown, MD. Pp. 526, indexed. ISSN 0889-4698.

This short volume reviews a wide range of quality issues from an American perspective.

The undoubted increase in patient safety in the last 20 yr has had many causes, but one may perhaps flag up two principal ones. The analysis of accidents, incidents, and patient deaths, promoted so successfully by the National CEPOD studies in the UK, and the Anesthesia Patient Safety Foundation in the USA, has introduced many changes in working practice The second major contribution to patient safety has been improved monitoring standards; it is well within living memory that one had no continuous monitoring available—an intermittent sphygmomanometer, a finger on the pulse, and a view of the moving bag to tell us of the condition of a patient covered by drapes John Eichhorn provides an excellent review of the role of monitoring in reducing risk in anaesthesia, and some of the difficulties in making an evidence-based assessment of the exact contribution that it has made to increasing safety.

There are a number of shorter articles on quality management, which I found a little uninspiring—neither convincing me that I should change my practice, nor that of our institution The data are US-based and reflect the political set-up in the USA rather than the UK. There are a number of points with which we are readily familiar, such as the importance of informed consent, good documentation, confidentiality etc., which are, of course, universal truisms, but I suppose a quality review could not be complete without mentioning them. There is, however, no solution provided to the difficulties of coping with inadequate information systems, missing notes, patients being admitted after lists have started etc., which all beset today's UK anaesthetists

A chapter on paediatric sedation outside the operating room reflects a practice rather different from that commonly found in the UK. As an example, midazolam 0.5 mg kg^{-1} was given to a child at home before a procedure; the child fell asleep in a car seat, became obstructed and died.

An interesting article on the difficult problem of outcome research in anaesthesia discusses study design, meta-analyses, and other ways of analysing data. I found this a useful chapter, though perhaps not quite as inspiring as the leading speakers in the UK would be.

The closed claims project does appear to have contributed towards improving outcomes, in the sense that it made people more aware of just how expensive anaesthetic accidents can be—biasing thought towards risk management rather than error management. They also demonstrated the advances in patient safety contributed by monitoring, where only 9% of the claims from the 1990s were preventable by monitoring, in contrast to 39% of the claims from the 1970s.

The book closes with short articles on anaesthesia simulation and expert witnesses.

Overall, I am not clear of the benefits of books of this type, which are essentially assemblies of review articles If I want to be better informed about a particular topic, I generally prefer to go straight to a literature search and read articles in the journals. However, this approach does perhaps provide a useful overview of the position at any one time, albeit from a transatlantic perspective.

J. A. Lack
Salisbury, UK

Basic Statistics and Epidemiology: A Practical Guide. (1st Edn). A. Stewart. Published by Radcliffe Medical Press, Oxford. Pp. 151; indexed. Price £19.95. ISBN 1-85775-589-8.

An understanding of statistical concepts and epidemiological methods has relevance to the established clinician, the novice researcher, and the FRCA candidate. The syllabus for the FRCA examination requires knowledge of study design and data collection methods, descriptive and inferential statistics, and an appreciation of their limitations. Knowledge of statistical and research methods may be tested in the primary OCSE, or may appear in the final FRCA short answer question or viva section. Anecdotal evidence would suggest that FRCA candidates are poorly prepared for these questions. For the anaesthetist attempting to follow the evidence-based medical approach, the novice researcher and the time-pressed examination candidate, a concise, succinct overview is required. Unfortunately, this short book does not meet any of these needs.

No prior knowledge is assumed by the author, as is illustrated by the 'What are statistics?', and 'What is epidemiology?' chapters. The early chapters on statistics give a good introduction, with descriptions of sampling methods, types of data, and presentation techniques. These are short, easily digested sections, which are well presented. The following chapters are less clear, with cumbersome descriptions and often unnecessary calculations. There are few diagrams and the use of bullet points and summary tables is poor. The progression through the chapters is neither smooth nor logical; notably the concept of frequency distributions is introduced too late in the text. Correlation, linear regression, and analysis of variance are given just a cursory reference. Nonparametric methods and the transformation of data are simply not described.

Throughout the statistics chapters, the author often reminds the reader that he is consulting a 'basic text', and regularly redirects him to other sources of information. This first section of the book feels very much like an 'add-on' to the later chapters and gives way to what appears as the book's strength: the epidemiological methods. Bias, incidence, prevalence, standardization, risk, and causality are clearly outlined. The benefits and limitations of different study designs are summarized in well-structured chapters. The over-hyped issue of multiple comparisions and testing is conveniently sidestepped. The requirements of a screening programme are detailed, although this is largely by repetition of the UK national screening committee's criteria. Subjects that are given quite limited consideration are: clinical trial planning; the calculation of sample sizes; and the roles of ethics and consent in medical research. An appreciation of power and sample size estimations leads to an understanding of statistical principles, and of the relative importance of statistical and clinical significance.

Overall, this book does what it says on the cover, in that it is *basic*. It covers much ground with inadequate detail and unclear explanations. Information is poorly summarized and key subject areas are neglected. It is more suited to students or those with a passing interest in this area, and at less than £20, it should be considered As for readers of the *BJA*, better books addressing statistical and mathematical principles specifically aimed at anaesthetists have been reviewed in recent years. So although there will be a readership for this book, unfortunately it fails to achieve *significance* in reaching the anaesthetic bookshelf!

G. L. Thomas and M. O. Columb
Manchester, UK

International Anesthesiology Clinics. W. E. Hurford (editor-in-chief). Vol. 40: Number 2: 2002: *Preoperative Evaluation and Cost Containment.* R. A. Wiklund (editor). Published by Lippincott, Williams and Wilkins, Philadelphia. Pp. 212; indexed; illustrated. ISSN 0020-5907.

This volume, *Preoperative Evaluation and Cost Containment,* is a multi-author book produced in the standard format of the *International Anesthesiology Clinics* series. The editor's goal has been 'to provide the reader with a broad view of the diverse issues related to preanesthetic assessment, with special consideration to the cost-effectiveness of these issues' He has achieved this in 15 chapters, with contributions from 23 authors.

In the first two chapters, Drs Archer, Schmiesing, Macario and Gibby have made a strong case for anaesthesia-led preoperative assessment clinics. Preoperative assessment is discussed as a quality improvement issue that demands the support of the whole institution. The cost–benefit ratio has been examined and these authors have concluded that preoperative clinics led by an anaesthetic team are cost effective, and result in efficient organization and utilization of operating theatre time.

The following chapter is a summary of the recently published ASA Practice Advisory for Preanesthetic Evaluation (*Anesthesiology* 2002, **96**: 485–96) The author, Dr Pasternak, who chaired the ASA Preoperative Evaluation Task Force, cites many reports to support his claim that whenever preoperative assessment has been carried out by anaesthetists, the number of investigations ordered and referrals to other specialists have been fewer than when surgeons carry it out.

The remaining chapters are reviews of various clinical topics. The chapters on postoperative nausea and vomiting, glycaemic management of diabetes in the perioperative setting, transfusion medicine in the preoperative period, and the role of the anaesthetist in the antenatal period, are good summaries but contain nothing new for most anaesthetists. However, the update on the American Heart Association/American College of Cardiology (AHA/ACC) guidelines on evaluation of the cardiac patient undergoing non-cardiac surgery, and the review of perioperative use of β-blockers in reducing cardiac risk, are comprehensive and informative.

The twelfth chapter is on paediatric preoperative assessment, which is a good overview for the occasional paediatric anaesthetist. One chapter is reserved for the use of computers for preoperative assessment. Dr Bader discusses the problems involved in using this technology, particularly the issue of maintaining patient confidentiality, and offers some solutions. She also provides some web addresses (www.smartsleep com; www.healthquiz.com), that have some demonstrations on internet-based preoperative assessment programmes.

The final chapter considers 'holistic issues in the preoperative period'. Reading it reminded me of sitting in a community health lecture in medical school in Ghana, listening to a sociology lecturer talking about the 'sick-role, family support, spirituality, beliefs and emotions'. The author of this chapter, Dr Kraft, emphasizes that if these aspects of humanity are addressed during the preoperative period, patient confidence increases, while decreasing anxiety, analgesic requirement, and hospital stay. There can be no more inexpensive method of containing perioperative cost than this.

I enjoyed reading this book. It is a slim volume, readable in a couple of evenings. The topics discussed are interesting, well referenced, and up-to-date. I was, however, disappointed that the topic of preoperative assessment clinics was not discussed by a truly international forum. Preoperative outpatient clinics were first proposed over 50 yr ago by Dr J. Alfred Lee (*Anaesthesia* 1949; **4**:168–74), but the concept is still not fully embraced. What we have here is only the USA experience. It would have been interesting to read what other countries' experiences are. With the current trend of ambulatory surgery and 'same day admit' inpatients, seeing patients in the preoperative clinic seems to be the way forward.

This book will be of interest to most anaesthetists. Clinical directors and theatre managers will find the first three chapters particularly helpful. According to chapter two, they will help them explain 'how preoperative assessment programs can be justified financially to hospital administrators'.

J. Appiah-Ankam
Liverpool, UK

British Journal of Anaesthesia 89 (6): 945–54 (2002)

VOLUME 89 • AUTHOR INDEX

Abdel-El Fattah A *see* Lowe PR **199P**
Adam F *see* Menigaux C **857**
Addy V *see* Edge CJ **514**
Adsetts D *see* Dobbs P **353P**, Dobbs P **353P**
Agnew N *see* Kendall J **203P**
Ai K *see* Serita R **896**
Akcora D *see* Telci L **594**
Akintürk H *see* Müller M **398**
Akpir K *see* Telci L **594**; Senturk M **849**
Akrofi M *see* Kendall J **203P**
Alahuhta S *see* Ala-Kokko TI **438**
Ala-Kokko TI, Karinen J, Räihä E, Kiviluoma K and **Alahuhta S** Pharmacokinetics of 0.75% ropivacaine and 0.5% bupivacaine after ilioinguinal-iliohypogastric nerve block in children **438**
Alexander JI Key Topics in Chronic Pain: *book review* **193**
Allaouchiche B *see* Duflo F **231**
Allen SA *see* Olufolabi AJ **652**
Allen SJ, Gormley SMC, Elliott P, Armstrong MA, Baker RC, McMurray TJ and **McBride WT** Urinary TGF-β is elevated following cardiac surgery and is reduced following methylprednisolone administration. *abstract* **195P**
Allsop P *see* Tivey M **349P**
Allsop P, Prince J, Hardiman C, Poxon I, Coates S, Tivey M, Cunningham MJ and **Stenhouse CW** A hospital-wide in-patient survey of level of care delivery: preliminary results: *abstract* **349P**
Alston RP Cardiogenic Shock: Diagnosis and Treatment: *book review* **665**
Anderson JAM *see* Doman RJP **524**
André E *see* Ryckwaert F **599**
Anslow P *see* Edge CJ **514**
Antkowiak B *In vitro* networks: cortical mechanisms of anaesthetic action **102**
Antognini JF and **Carstens E** *In vivo* characterization of clinical anaesthesia and its components **156**
Apfel CC *see* Maleck WH **339**
Appadurai IR, Hanna L, Fitz-Henry J, Chan S and **Symonds RP** Analgesia for pelvic brachytherapy *correspondence* **342**
Appiah-Ankam J International Anesthesiology Clinics Preoperative Evaluation and Cost Containment· *book review* **943**
Aps C Postoperative critical care: overnight intensive recovery: *correspondence* **344**
Armbruster W *see* Eikermann M **277**
Armfield A *see* Kannan S **512**
Armstrong MA *see* Allen SJ **195P**; Bedi A **546**
Arrowsmith JE Anesthesia for the Cardiac Patient: *book review* **664**
Arrowsmith JE Shortage of isoproterenol (isoprenaline) hydrochloride: *correspondence* **528**
Asai T Confidence in statistical analysis: *editorial* **807**
Asai T, Kawashima A, Hidaka I and **Kawachi S** The laryngeal tube compared with the laryngeal mask· insertion, gas leak pressure and gastric insufflation **729**
Asai T, Matsumoto S and **Shingu K** Comparison of two Macintosh laryngoscope blades *abstract* **670P**
Ateleanu B *see* Daoud Z **442**; Sudheer PS **674P**
Athanassiou L *see* Stacey M **196P**
Attallah F *see* Subramaniam R **188**
Aubrun F *see* Paqueron X **697**
Aziz S and **Stables RH** The Year in Interventional Cardiology. 2002: *book review* **665**

Backe SK and **Lyons GR** High-dose tinzaparin in pregnancy and the need for urgent delivery **331**
Baker DJ Management of casualties from terrorist chemical and biological attack a key role for the anaesthetist. *editorial* **211**
Baker DJ Problems in Anesthesia Series *book review* **530**
Baker RC *see* Allen SJ **195P**
Banerjee TP, Nimmo AF and **Drummond GB** Influence of oxygen therapy on heart rate after abdominal surgery: *abstract* **673P**
Barberis C *see* Ryckwaert F **599**
Barclay PM *see* Cowan CM **452**
Barker A *see* Turnbull D **205P**
Barker GL *see* Patil V **586**
Barrington J *see* Rousseau GF **846**
Barton RL *see* Simpson TP **382**
Bastien O *see* Piriou V **486**
Batson S *see* Olvera C **351P**
Baudouin SV *see* Burn L **350P**
Baxendale BR *see* Moppett IK **204P**; Moppett IK **358P**
Baxter P *see* Coomber S **873**
Beard D *see* Graham CA **659**
Beavis SE and **Spittle CSN** Tracheostomy management after intensive care a survey of current practice in the UK. *abstract* **350P**
Beckingham IJ *see* Eastwood JR **201P**
Beddow ECL *see* Makings EA **356P**
Bedi A *see* Walsh SJ **799**
Bedi A, McBride WT, Armstrong MA, Murray JM and **Fee JPH** Xenon has no effect on cytokine balance and adhesion molecule expression within an isolated cardiopulmonary bypass system **546**
Begg A *see* Drummond GB **200P**
Behnke H, Worthmann F, Cornelissen J, Kahl M and **Wulf H** Plasma concentration of ropivacaine after intercostal blocks for video-assisted thoracic surgery **251**
Bellamy M *see* Mahadeva S **650**
Bellingan G *see* Hails J **354P**
Bellingan GJ *see* Olvera C **351P**
Beloeil H, Corsia G, Coriat P and **Riou B** Remifentanil compared with sufentanil during extra-corporeal shock wave lithotripsy with spontaneous ventilation: a double-blind, randomized study **567**
Belton O *see* Leonard IE **206P**
Benjamin N *see* Makings EA **356P**
Benson M *see* Muller M **398**
Berkenstadt H, Loebstein R, Faibishenko I, Halkin H, Keidan I and **Perel A** Effect of a single dose of esmolol on the bispectral index scale (BIS) during propofol/fentanyl anaesthesia **509**
Bertaccini E *see* Trudell JR **32**
Blackman DJ *see* Edge CJ **788**
Bland JM *see* Dolin SJ **409**
Blanloeil Y *see* Walsh EM **184**
Bleckwenn M *see* Urban BW **3**
Bogod D *see* Sherman RW **687**
Boiteau HL *see* Lejus C **693**
Boldt J, Haisch G, Suttner S, Kumle B and **Schellhaass A** Effects of a new modified, balanced hydroxyethyl starch preparation (Hextend®) on measures of coagulation **722**
Bolger C *see* Kevin LG **551**
Bonde J *see* Due V **919**
Bonner S *see* Easby J **354P**
Bonnette P *see* Dalibon N **930**
Boscoe MJ *see* Lovell AT **194P**
Boselli E *see* Cannesson M **925**
Bouhemad B, Langeron O, Orliaguet G, Coriat P and **Riou B** Effects of halothane and isoflurane on the contraction, relaxation and energetics of rat diaphragmatic muscle **479**
Bourgain JL *see* Patel A **184**
Bowhay A Pediatric Anesthesia· Principles and Practice: *book review* **191**
Bowie RA *see* Sherman RW **687**
Boylan JF *see* McCaul C **766**
Bradford A *see* Leonard IE **206P**
Bradford C *see* Burn L **350P**
Brand M *see* Coluzzi F **352P**
Bräu M *see* Muller M **398**
Brealey D *see* Coluzzi F **352P**
Brennan FM *see* Robertshaw HJ **676P**
Bricard H *see* Yvon A **888**

© The Board of Management and Trustees of the British Journal of Anaesthesia

Brill S, **Sedgwick PM**, **Hamann W** and **di Vadi PP** Efficacy of intravenous magnesium in neuropathic pain **711**
Brimacombe J *see* O'Neil MJ **936**
Brohi FA, **Djurberg HG** and **Rowney DA** Cerebrovascular carbon dioxide reactivity in children anaesthetized with sevoflurane: *correspondence* **525**
Bromm B *see* Detsch O **294**
Brooks A and **Riley B** Missed injury in major trauma in the adult intensive care unit: *abstract* **351P**
Brooks A *see* Eastwood JR **201P**
Brough SJ *see* Jerman JC **882**
Brunner MD, **Nel MR**, **Fernandes R**, **Thornton C** and **Newton DEF** Auditory evoked response during propofol anaesthesia after pre-induction with midazolam **325**
Bryssine B *see* Cannesson M **925**
Burbridge K, **Rudge C** and **Park GR** The pattern of organ donation after CVA from ICUs in the UK in the last 7 yr. *abstract* **359P**
Burbridge K, **Rudge C** and **Park GR** The pattern or organ donation after trauma from ICUs in the UK in the last 7 yr: *abstract* **360P**
Burn L, **Foster K**, **Maddison V**, **Bradford C** and **Baudouin SV** Is the ACP data set accurate? A network-based survey *abstract* **350P**
Butler SR *see* Simpson TP **382**

Camci E *see* Senturk M **849**
Campbell K *see* Millo J **358P**
Canbolat AT *see* Telci L **594**
Cannesson M, **Nargues N**, **Bryssine B**, **Debon R**, **Boselli E** and **Chassard D** Intrathecal morphine overdose during combined spinal–epidural block for Caesarean delivery **925**
Capan LM *see* Sandhu NS **254**
Carli F *see* Loughnan BA **466**
Carmichael RL *see* Galley HF **198P**
Carr J *see* Tivey M **349P**
Carstens E *see* Antognini JF **156**
Cashman JN *see* Dolin SJ **409**
Censier K *see* Girard T **571**
Chan LC *see* Innerhofer P **934**
Chan S *see* Appadurai IR **342**
Chang Y, *see* Martyn JAJ **580**
Charlton GA *see* Olufolabi AJ **652**
Charters P *see* Lam YF **204P**; Groom P **205P**; Halligan M **671P**
Chassard D *see* Duflo F **231**; Cannesson M **925**
Chassot PG, **Delabays A** and **Spahn DR** Preoperative evaluation of patients with, or at risk of, coronary artery disease undergoing non-cardiac surgery **747**
Chauvin M *see* Menigaux C **857**
Chawathe MS, **Hall JE**, **Mecklenburgh JS** and **Jones RM** BIS—cautionary interpretation of data in children. *abstract* **672**
Chelly JE *see* Doursout MF **492**
Chêne G *see* Forestier F **715**
Chiari P *see* Pinou V **486**
Clarke FC *see* Easby J **354P**
Clayton JA and **Shelly MP** Atlas of Hemofiltration: *book review* **191**
Clergue F *see* Garnerin P **633**
Coad N *see* Macnaughton PD **355P**
Coates S *see* Allsop P **349P**
Coates SJ *see* Tivey M **349P**
Cohen A *see* Mahadeva S **650**
Col T *see* Heidegger T **863**
Coiffic A *see* Forestier F **715**
Collis RE *see* Daoud Z **442**
Colson P *see* Ryckwaert F **599**
Columb MO *see* Thomas GL **943**
Coluzzi F, **Brealey D**, **Brand M** and **Singer M** Comparison of aconitase activity in patients and a rat model of septic shock: *abstract* **352P**
Conway D *see* Macnab WR **355P**; Roberts H **363P**
Cook TM *see* Twigg SJ **786**
Coomber S, **Todd C**, **Park G**, **Baxter P**, **Firth-Cozens J** and **Shore S** Stress in UK intensive care unit doctors **873**
Cooper GM *see* Thomas TA **499**
Cooper GM, **Lewis G** and **Neilson J** Confidential enquiries into maternal deaths, 1997–1999 *editorial* **369**
Cope T *see* McCrossan L **194P**
Cordingley JJ *see* Robb JD **352P**
Coriat P *see* Bouhemad B **479**; Beloeil H **567**; Paqueron X **697**
Cornelissen J *see* Behnke H **251**
Corsia G *see* Beloeil H **567**
Costa MG *see* Linton NWF **336**
Cowan C *see* McCrossan L **194P**
Cowan CM, **Kendall JB**, **Barclay PM** and **Wilkes RG** Comparison of intrathecal fentanyl and diamorphine in addition to bupivacaine for Caesarean section under spinal anaesthesia **452**
Cross RA *see* Macnab WR **355P**
Cunningham AJ *see* Kevin LG **551**; Kevin LG **658**; Leonard IE **206P**
Cunningham MJ *see* Allsop P **349P**; Tivey M **349P**
Cuthbertson BH, **Stott SA** and **Webster NR** Exhaled nitric oxide as a marker of lung injury in coronary artery bypass surgery **247**

Dakin J *see* Robb JD **352P**
Dalibon N, **Stern M**, **Bonnette P**, **Dreyfus G** and **Fischler M** Probable allergic reaction to cyclosporin and early formation of thrombi on a pulmonary artery catheter. two unusual complications during bilateral lung transplantation **930**
Daoud Z, **Collis RE**, **Ateleanu B** and **Mapleson WW** Evaluation of S1 motor block to determine a safe, reliable test dose for epidural analgesia **442**
David AC, **Pilcher DV** and **Davidson AC** Survival and success of weaning from prolonged ventilation· *correspondence* **938**
David JS *see* Pinou V **486**
Davidson AC *see* David AC **938**; Pilcher DV **361P**; Pilcher DV **362P**
Davies JA *see* Moppett IK **204P**
Davies JR Safer labelling of levobupivacaine· *correspondence* **345**
Davies R *see* Subbe CP **365P**
Davis JB *see* Jerman JC **882**
Dawson S *see* Wasson CMA **367P**
Debon R *see* Cannesson M **925**; Duflo F **231**
Decorps M *see* Julien-Dolbec C **287**
Delabays A *see* Chassot PG **747**
Della Rocca G *see* Linton NWF **336**
Detsch O *see* Vahle-Hinz C **123**
Detsch O, **Kochs E**, **Siemers M**, **Bromm B** and **Vahle-Hinz C** Differential effects of isoflurane on excitatory and inhibitory synaptic inputs to thalamic neurones *in vivo* **294**
Deusch E *see* Krenn H **637**; Sator-Katzenschlager S **764**
di Vadi PP *see* Brill S **711**
Dilger JP The effects of general anaesthetics on ligand-gated ion channels **41**
Dinsmore J *see* Jones SJ **762**
Djurberg HG *see* Brohi FA **525**
Dobbs P, **Stubbins K**, **Adsetts D** and **Leggott S** Can an early warning scoring system identify physiological deterioration in patients who later suffer a cardiac arrest?: *abstract* **353P**
Dobbs P, **Stubbins K**, **Leggott S** and **Adsetts D** A prospective audit of the incidence of physiological monitoring in the 24 h before a cardiac arrest in a district general hospital: *abstract* **353P**
Dodds C The Electronic Anesthesiology Library (TEAL) on CD-ROM: *CD review* **940**
Doepp F *see* Schreiber SJ **769**
Dolezal S *see* Sator-Katzenschlager S **764**
Dolin SJ Concise Anatomy for Anaesthesia. *book review* **346**
Dolin SJ, **Cashman JN** and **Bland JM** Effectiveness of acute post-operative pain management· I. Evidence from published data **409**
Dolling M, **Roberts N** and **Sharpe P** The effectiveness of the Neuropen in predicting the dermatomal limits of sensory blockade in regional anaesthesia for Caesarean section as compared with ethyl chloride *abstract* **680P**
Dolling M, **Sharpe P** and **Hanning CD** Change in snoring as a predictive factor for pre-eclampsia *abstract* **678P**
Donald S *see* O'Neil MJ **936**
Donati F *see* Laurin J **832**
Doré CJ *see* Loughnan BA **466**
Dorman RIP, **Anderson JAM** and **Saenko EL** Hirudin and its reversal. *correspondence* **524**
Doursout MF, **Joseph PM**, **Liang YY**, **Hartley CJ** and **Chelly JE** Role of propofol and its solvent, intralipid, in nitric oxide-induced peripheral vasodilatation in dogs **492**
Dreyfus G *see* Dalibon N **930**

Droghetti L, Giganti M, Memmo A and **Zatelli R** Air embolism: diagnosis with single-photon emission tomography and successful hyperbaric oxygen therapy **775**

Drummond GB *see* Banerjee TP **673P**; Knaggs CL **673P**; Prasad CV **209P**

Drummond GB, Begg A and **Tiplady B** Electronic diary records show similar symptom severity after major and intermediate gynaecological surgery· *abstract* **200P**

Drury PME Notable Names in Anaesthesia: *book review* **805**

Ducouret P *see* Yvon A **888**

Due V, Bonde J, Espersen K, Jensen TH and **Perner A** Lactic acidosis in the rectal lumen of patients with septic shock measured by luminal equilibrium dialysis **919**

Duflo F, Debon R, Goudable J, Chassard D and **Allaouchiche B** Alveolar and serum oxidative stress in ventilator-associated pneumonia **231**

Duggan JE *see* Zimmer CR **203P**

Dunsire MF *see* O'Leary M **937**

Duxbury MS and **Walker MB** A survey of the use of intracranial pressure monitoring in non-neurosurgical centres. *abstract* **366P**

Easby J, Clarke FC, Bonner S and **Lawler PG** Secondary inter-hospital transfers of critically ill patients: completing the audit cycle: *abstract* **354P**

Eastwood JR, Brooks A, Beckingham IJ and **Girling KJ** Use of the Paratrend© sensor to measure the partial pressures of oxygen and carbon dioxide in the liver tissue of patients undergoing liver resection: *abstract* **201P**

Eberhart LHJ, Morin AM, Wulf H and **Geldner G** Patient preferences for immediate postoperative recovery **760**

Eberli FR *see* Wahl A **519**

Eddleston J *see* Roberts H **363P**

Edge CJ, Blackman DJ, Gupta K and **Sainsbury M** General anaesthesia in a patient with Brugada syndrome **788**

Edge CJ, Hyman N, Addy V, Anslow P, Kearns C, Stacey R and **Waldmann C** Posterior spinal ligament rupture associated with laryngeal mask insertion in a patient with undisclosed unstable cervical spine **514**

Edmondson L *see* Zimmer CR **203P**

Eikermann M, Hunkemöller I, Peine L, Armbruster W, Stegen B, Hüsing J and **Peters J** Optimal rocuronium dose for intubation during inhalation induction with sevoflurane in children **277**

Ekouevi D *see* Forestier F **715**

El Sakka NE, Galley HF, Lowe PR and **Webster NR** Genetic analysis of the MnSOD gene in patients with sepsis: *abstract* **199P**

Ellinger K *see* Genzwuerker HV **733**

Elliott P *see* Allen SJ **195P**

Engelhardt T, Galley HF and **Webster NR** 7-Nitroindazole reduces spontaneous activity in wild-type and nitric oxide synthase type 1 gene-deleted mice· *abstract* **202P**

Engelhardt T, Galley HF, MacLennan FM and **Webster NR** Saliva cyclic GMP increases during anaesthesia **635**

Engelhardt T, Lowe PR, Galley HF and **Webster NR** 7-Nitroindazole reduces the MAC of isoflurane in wild-type and type 1 nitric oxide synthase knockout mice: *abstract* **201P**

Erden T *see* Telci L **594**

Esen F *see* Telci L **594**

Espersen K *see* Due V **919**

Evans TW *see* Robb JD **352P**

Faibishenko I *see* Berkenstadt H **509**

Falcus J *see* Subbe CP **365P**

Faseri A *see* Heidegger T **863**

Fasting S and **Gisvold SE** Equipment problems during anaesthesia—are they a quality problem? **825**

Fee JPH *see* Bedi A **546**

Fenton R *see* Sampathkumar S **202P**

Fernandes R *see* Brunner MD **325**

Fernando R *see* Patel N **679P**

Fettes PDW *see* Serpell MG **800**; Shankar R **662**

Finlayson J *see* Ruttmann TG **226**

Firth-Cozens J *see* Coomber S **873**

Fischler M *see* Dalibon N **930**

Fitzgerald D *see* Leonard IE **206P**

Fitzgerald RD *see* Krenn H **637**

Fitz-Henry J *see* Appadurai IR **342**

Flückiger K *see* Heidegger T **863**

Foëx P the Year in Hypertension 2001: *book review* **191**

Forestier F, Coiffic A, Mouton C, Ekouevi D, Chêne G and **Janvier G** Platelet function point-of-care tests in post-bypass cardiac surgery are they relevant? **715**

Forootan B and **Karimi N** Intrathecal metoclopramide reduces intrathecal meperidine induced nausea and vomiting in surgical patients: *abstract* **208P**

Forshaw S *see* Vaughan STA **674P**

Foster K *see* Burn L **350P**

Fouquet N *see* Pain L **614**

Fournier R, Van Gessel E, Weber A and **Gamulin Z** Epinephrine and clonidine do not improve intrathecal sufentanil analgesia after total hip replacement **562**

Fox R *see* Marchant WA **644**

Francis S, Russell WC and **Thompson JP** Complete airway obstruction in a ventilated patient after oesophageal dilation **517**

Franks NP *see* Ma D **739**

Fransson SG *see* Savage R **185**

Fries D *see* Innerhofer P **934**

Fryer JM *see* Vaughan STA **674P**

Fuchs J *see* Schummer W **335**

Galley HF *see* El Sakka NE **199P**; Engelhardt T **635**; Lowe PR **199P**; Engelhardt T **201P**; Engelhardt T **202P**

Galley HF, Lowe PR, Carmichael RL and **Webster NR** Genotype and IL-10 response during cardiopulmonary bypass *abstract* **198P**

Gamulin Z *see* Fournier R **562**

Gao F *see* Perkins GD **360P**; Perkins GD **405**; Sutton P **366P**

Garnerin P, Schiffer E, Van Gessel E and **Clergue F** Root-cause analysis of an airway filter occlusion. a way to improve the reliability of the respiratory circuit **633**

Ge SJ, Zhuang XL, Wang YT, Wang ZD and **Li HT** Changes in the rapidly extracted auditory evoked potentials index and the bispectral index during sedation induced by propofol or midazolam under epidural block **260**

Geary U Accident and Emergency Diagnosis and Management *book review* **530**

Gelbinger C *see* Heidegger T **863**

Geldner G *see* Eberhart LHJ **760**

Gemmel L *see* Subbe CP **365P**, Subbe CP **365P**

Genzwuerker HV, Vollmer T and **Ellinger K** Fibreoptic tracheal intubation after placement of the laryngeal tube **733**

Gérard J-L *see* Yvon A **888**

Germann R *see* Heidegger T **863**

Giganti M *see* Droghetti L **775**

Giles S *see* Perkins GD **360P**; Sutton P **366P**

Gillies DF *see* Lam YF **204P**; Groom P **205P**

Girard T, Treves S, Censier K, Mueller CR, Zorzato F and **Urwyler A** Phenotyping malignant hyperthermia susceptibility by measuring halothane-induced changes in myoplasmic calcium concentration in cultured human skeletal muscle cells **571**

Girling KJ *see* Eastwood JR **201P**

Gisvold SE *see* Fasting S **825**

Goddard JM *see* Johnson TN **428**

Goldfrad C *see* Stenhouse C **364P**

Goldhill DR and **McNarry A** The longer the patient is in hospital before ICU admission the higher the mortality *abstract* **356P**

Goldhill DR *see* McNarry A **357P**

Goodman NW *see* Pickard S **804**

Gopal S and **Stenhouse CW** Observations in 50 consecutive medical admissions to an adult intensive care unit in a district general hospital-an admission diagnosis of respiratory failure does not affect the likelihood of monitoring ventilatory frequency and oxygen saturation: *abstract* **364P**

Gordon AC *see* Peters CJ **361P**

Gordon H *see* Loughnan BA **466**

Gormley SMC *see* Allen SJ **195P**

Gornall CB *see* Moppett IK **196P**

Gorton H Shnider and Levinson's Anesthesia for Obstetrics· *book review* **192**

Goudable J *see* Duflo F **231**

Goudsouzian NG *see* Martyn JAJ **580**
Gould TH, Grace K, Thorne G and **Thomas M** Effect of thoracic epidural anaesthesia on colonic blood flow **446**
Grace K *see* Gould TH **446**
Graf J *see* Janssens U **237**
Graham CA, Beard D and **McKeown DW** Airway management in the emergency department: *correspondence* **659**
Gray J *see* Jerman JC **882**
Greaves D Prescription for Learning: *book review* **347**
Greer R *see* Wasson CMA **367P**
Grobbee DE *see* van Klei WA **221**
Groesdonk H *see* Janssens U **237**
Groom P *see* Lam YF **204P**
Groom P, Johnstone J, Charters P, Lam YF and **Gillies DF** The effect of airway manoeuvres and route of respiration on spatial orientation of the upper airway. *abstract* **205P**
Grubmüller R *see* Sator-Katzenschlager S **764**
Gucyetmez B *see* Senturk M **849**
Guignard B *see* Menigaux C **857**
Guillon G *see* Ryckwaert F **599**
Gupta K *see* Edge CJ **788**
Gustafsson U *see* McNamee DA **702**

Hack H, Kannan S and **Sherwood N** The output of two sevoflurane vaporizers in the presence of helium: *correspondence* **797**
Hadley J *see* Makings EA **356P**
Hails J, Kwaku F, Wilson APR, Bellingan G and **Singer M** Large variation in MRSA policies, procedures, and prevalence in English intensive care units. A questionnaire analysis: *abstract* **354P**
Haisch G *see* Boldt J **722**
Håkanson E *see* Savage R **185**
Halkin H *see* Berkenstadt H **509**
Hall GM *see* Nicholson G **904**
Hall JE *see* Chawathe MS **672P**; Jeffs SA **424**; Raj N **675P**; Sudheer PS **674P**; Wilkes AR **670P**
Hall NA *see* Schupp M **678P**
Halligan M, Weldon B and **Charters P** A clinical appraisal of the Bonfils Intubating Fibrescope: *abstract* **671P**
Halpern S *see* van der Vyver M **459**
Hamann W *see* Brill S **711**
Hamid S *see* Pilcher DV **361P**, Pilcher DV **362P**
Hancock SM *see* Moppett IK **196P**
Hanks R *see* Stenhouse C **364P**
Hanna L *see* Appadurai IR **342**
Hanning CD *see* Dolling M **678P**
Hanouz J-L *see* Yvon A **888**
Hanrath P *see* Janssens U **237**
Hardiman C *see* Allsop P **349P**
Hariprasad M and **Smurthwaite GJ** Management of a known difficult airway in a morbidly obese patient with gross supraglottic oedema secondary to thyroid disease **927**
Harmer M *see* Sudheer PS **674P**, Raj N **675P**
Harper SJ *see* Jones AG **526**
Harris DNF *see* Lovell AT **194P**
Harris P *see* Tivey M **349P**
Hartley CJ *see* Doursout MF **492**
Hartsilver E *see* Phillips JMG **778**
Harwood RJ *see* Patil V **586**
Headley PM *see* Pickering AE **207P**
Heidegger T, Husemann Y, Nuebling M, Morf D, Sieber T, Huth A, Germann R, Innerhofer P, Faserl A, Schubert C, Geibinger C, Flückiger K, Coi T and **Kreienbühl G** Patient satisfaction with anaesthesia care: development of a psychometric questionnaire and benchmarking among six hospitals in Switzerland and Austria **863**
Heinke W and **Schwarzbauer C** *In vivo* imaging of anaesthetic action in humans: approaches with positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) **112**
Heinze G *see* Sator-Katzenschlager S **764**
Helm M *see* Richards MJ **936**
Hempelmann G *see* Müller M **398**
Henderson KA *see* Raj N **675P**
Henfrey MME *see* Sherman RW **687**
Hidaka I *see* Asai T **729**
Hinchliffe D and **Norris A** Management of failed intubation in a septic parturient **328**
Hinchliffe D *see* O'Leary M **937**
Hinds CJ *see* Makings EA **356P**; Peters CJ **361P**
Hirabayashi Y *see* Satoh M **641**
Hisano K *see* Shibano T **301**
Hodzovic I *see* Wilkes AR **671P**
Holte K, Sharrock NE and **Kehlet H** Pathophysiology and clinical implications of perioperative cluid excess **622**
Howard RF *see* Williams DG **839**
Howell SJ Clinical Data Interpretation in Anaesthesia and Intensive Care: *book review* **942**
Howie JC and **Tansey PJ** Blood transfusion in surgical practice—matching supply to demand. *editorial* **214**
Hua Y *see* Shibano T **301**
Hunkemöller I *see* Eikermann M **277**
Husemann Y *see* Heidegger T **863**
Hüsing J *see* Eikermann M **277**
Huth A *see* Heidegger T **863**
Hyman N *see* Edge CJ **514**
Hyvärinen A *see* Nieminen K **853**

Ilavajady S *see* Sennaraj B **473**
Innami Y *see* Serita R **896**
Innerhofer P *see* Heidegger T **863**
Innerhofer P, Fries D, Klingler A, Streif W, Ng KFJ, Lam CCK and **Chan LC** In vivo effect of haemodilution with saline on coagulation: *correspondence* **934**
Ion F Heal the Pain, Comfort the Spirit: *book review* **667**
Ishikawa S, Yokoyama K, Kuroiwa T and **Makita K** Apparent diffusion coefficient mapping predicts mortality and outcome in rats with intracerebral haemodynamic disturbance: potential role of intraoperative diffusion and perfusion weighted magnetic resonance imaging to detect cerebral ischaemia **605**

Jacobs P *see* Smart NG **186**
Jagan D *see* Sennaraj B **473**
James MFM *see* Ruttmann TG **226**
Janssens U, Groesdonk H, Graf J, Radke PW, Lepper W and **Hanrath P** Comparison of oesophageal and gastric air tonometry in patients with circulatory failure **237**
Janvier G *see* Forestier F **715**
Jeffs SA, Hall JE and **Morris S** Comparison of morphine alone with morphine plus clonidine for postoperative patient-controlled analgesia **424**
Jellinek H *see* Krenn H **637**
Jensen TH *see* Due V **919**
Jerman JC, Gray J, Brough SJ, Ooi L, Owen D, Davis JB and **Smart D** Comparison of the effects of anandamide at recombinant and endogenous rat vanilloid receptors **882**
Johnson TN, Rostami-Hodjegan A, Goddard JM, Tanner MS and **Tucker GT** Contribution of midazolam and its 1-hydroxy metabolite to preoperative sedation in children: a pharmacokinetic-pharmacodynamic analysis **428**
Johnstone J *see* Groom P **205P**
Joly V *see* Menigaux C **857**
Jones JP *see* Rao MP **362P**
Jones RM *see* Chawathe MS **672P**
Jones SJ and **Dinsmore J** Effect of diclofenac on cerebral blood flow velocity in patients with supratentorial tumours **762**
Joseph G *see* van der Vyver M **459**
Joseph PM *see* Doursout MF **492**
Julien-Dolbec C, Tropres I, Montigon O, Reutenauer H, Ziegler A, Decorps M and **Payen JF** Regional response of cerebral blood volume to graded hypoxic hypoxia in rat brain **287**
Junger A *see* Müller M **398**

Kahl M *see* Behnke H **251**
Kalkman CJ *see* van Klei WA **221**
Kane NM *see* Simpson TP **382**
Kannan S *see* Hack H **797**
Kannan S, Sherwood N and **Armfield A** Flow-by induced hypoventilation in high spinal cord lesions—report of two cases **512**

Karasawa F, **Okuda T**, **Mori T** and **Oshima T** Maintenance of stable cuff pressure in the Brandt^{TM} tracheal tube during anaesthesia with nitrous oxide **271**
Karimi N *see* Forootan B **208P**
Karinen J *see* Ala-Kokko TI **438**
Kawachi S *see* Asai T **729**
Kawashima A *see* Asai T **729**
Kearns C *see* Edge CJ **514**
Kehlet H *see* Holte K **622**
Keidan I *see* Berkenstadt H **509**
Keil AD *see* Orlikowski C **922**
Keller C *see* O'Neil MJ **936**
Kemmotsu O *see* Shibano T **301**
Kendall J, **Agnew N**, **Akrofi M**, **Tran J**, **Pennefather S** and **Russell G** The effect of ranitidine on gastro-oesophageal acid reflux and tracheal acid aspiration: a randomized study of patients in the thoracotomy position: *abstract* **203P**
Kendall JB *see* Cowan CM **452**
Kendig JJ *In vitro* networks: subcortical mechanisms of anaesthetic action **91**
Kevin LG and **Cunningham AJ** Interdisciplinary collaboration in anaesthesia research: *correspondence* **658**
Kevin LG, **Cunningham AJ** and **Bolger C** Comparison of ocular microtremor and bispectral index during sevoflurane anaesthesia **551**
Khaw KS *see* Ngan Kee WD **556**
Kidner K and **Laurence AS** Effectiveness of basic airway management by junior doctors: *abstract* **208P**
Kilinc K *see* Sayin MM **242**
King JM Anaesthesia for the High Risk Patient: *book review* **803**
Kini KJ *see* Sankar D **677P**
Kiviluoma K *see* Ala-Kokko TI **438**
Klingler A *see* Innerhofer P **934**
Knaggs CL and **Drummond GB** Influence of fresh gas and circuit on induction of anaesthesia with sevoflurane *abstract* **673P**
Knape JTA *see* van Klei WA **221**
Kochs E *see* Detsch O **294**
Kokki H *see* Nieminen K **853**
Konstantinov I *see* Savage R **185**
Kosugi S *see* Serita R **896**
Kotake Y *see* Serita R **896**
Kreienbühl G *see* Heidegger T **863**
Krenn H, **Deusch E**, **Jellinek H**, **Oczenski W** and **Fitzgerald RD** Remifentanil or propofol for sedation during carotid endarterectomy under cervical plexus block **637**
Krishnamurthy A *see* Rao MP **362P**
Krovvidi H, **Kulkarni PR** and **Morley A** Management of intraoperative pulmonary oedema in a child following systemic absorption of phenylephrine eyedrops: *correspondence* **343**
Kulkarni PR *see* Krovvidi H **343**
Kumle B *see* Boldt J **722**
Kuroiwa T *see* Ishikawa S **605**
Kwaku F *see* Hails J **354P**
Kwapisz MM *see* Müller M **398**
Kwok HF, **Mills GH**, **Mahfouf M** and **Linkens DA** Non-invasive estimation of shunt: comparison of different hypoxaemia indices: *abstract* **206P**

Lack JA Problems in Anesthesia Series Quality, Safety, Risk and Outcomes: *book review* **942**
Lack JA *see* Thoms GMM **917**
Lam CCK *see* Innerhofer P **934**
Lam YF *see* Groom P **205P**
Lam YF, **Gillies DF**, **Charters P** and **Groom P** Determining natural variation through eigenvector projections in the human airway: *abstract* **204P**
Lambert B *see* Rao MP **362P**
Lambert UKW *see* Schreiber SJ **769**
Langeron O *see* Bouhemad B **479**; Paqueron X **697**
Latto IP *see* Wilkes AR **671P**
Launoy A *see* Pain L **614**
Laurence AS *see* Kidner K **208P**; Vaughan STA **674P**
Laurin J, **Donati F** and **Varin F** Stereoselective *in vitro* degradation pattern of mivacurium in human plasma **832**
Lawler PG *see* Easby J **354P**
Lawler PG Uncommon Problems in Intensive Care *book review* **346**
Le Cras AE *see* Lowe PR **199P**
Le Roux C *see* Lejus C **693**
Lee BB *see* Ngan Kee WD **556**
Legendre E *see* Lejus C **693**
Leggott S *see* Dobbs P **353P**; Dobbs P **353P**
Lehot JJ *see* Piriou V **486**
Lejus C, **Le Roux C**, **Legendre E**, **Renaudin M**, **Bolteau HL** and **Pinaud M** Fluoride excretion in children after sevoflurane anaesthesia **693**
Leonard IE, **Belton O**, **Bradford A**, **Fitzgerald D** and **Cunningham AJ** Investigation of the role of cyclooxygenase-2 in modulation of the pulmonary vascular response to chronic hypoxia: *abstract* **206P**
Lepper W *see* Janssens U **237**
Leuwer M *see* McCrossan L **194P**
Levack P Live and let die? A structured approach to decision-making about resuscitation. *editorial* **683**
Lewis G *see* Cooper GM **369**
Lhuillier F *see* Piriou V **486**
Li HT *see* Ge SJ **260**
Liang YY *see* Doursout MF **492**
Lin ES Fundamental Principles and Practice of Anaesthesia *book review* **940**
Linkens DA *see* Kwok HF **206P**
Linton NWF, **Linton RAF**, **Della Rocca G** and **Costa MG** Is comparison of changes in cardiac output, assessed by different methods, better than only comparing cardiac output to the reference method? *correspondence* **336**
Linton RAF *see* Linton NWF **336**
Lockey D Safe Retrieval and Transfer: the Practical Approach. *book review* **190**
Lockey DJ *see* Richards MJ **936**
Lockwood G Expansion of air bubbles in aqueous solutions of nitrous oxide or xenon **282**
Lockwood GG *see* Sampathkumar S **202P**
Loebstein R *see* Berkenstadt H **509**
Logan SW *see* Sudheer PS **674P**
Loufoua J *see* Piriou V **486**
Loughnan B Handbook of Obstetric Anaesthesia: *book review* **531**
Loughnan BA, **Carli F**, **Romney M**, **Doré CJ** and **Gordon H** Epidural analgesia and backache: a randomized controlled comparison with intramuscular meperidine for analgesia during labour **466**
Lovell AT, **Harris DNF** and **Boscoe MJ** Non-cerebral release of S100β during coronary artery bypass grafting: *abstract* **194P**
Lowe PR *see* Galley HF **198P**; El Sakka NE **199P**; Engelhardt T **201P**
Lowe PR, **Galley HF**, **Le Cras AE**, **Abdel-El Fattah A** and **Webster NR** Genetic analysis of TREM-1: a novel inflammatory receptor: *abstract* **199P**
Lowry KG *see* Macnaughton PD **355P**
Lowson SM Comparison of flow guided versus conventional volume replacement in major elective surgery: *abstract* **674P**
Luginbühl M *see* Wahl A **519**
Luginbühl M, **Reichlin F**, **Sigurdsson GH**, **Zbinden AM** and **Petersen-Felix S** Prediction of the haemodynamic response to tracheal intubation: comparison of laser-Doppler skin vasomotor reflex and pulse wave reflex **389**
Lumbroso A *see* Paqueron X **697**
Lynch L *see* Seymour AH **661**
Lyons G *see* Marchant W **525**
Lyons GR *see* Backe SK **331**

Ma D, **Wilhelm S**, **Maze M** and **Franks NP** Neuroprotective and neurotoxic properties of the 'inert' gas, xenon **739**
Ma KC *see* Ngan Kee WD **556**
MacKillop A *see* Vaughan STA **674P**
Mackinnon S *see* Naik P **359P**
MacLennan FM *see* Engelhardt T **635**
Macnab WR, **Cross RA** and **Conway D** Advanced directive questionnaire survey of intensive care staff: *abstract* **355P**
Macnaughton PD and **Watson GW** How effective are lung recruitment manoeuvres in acute lung injury: *abstract* **356P**
Macnaughton PD, **Lowry KG** and **Coad N** Use of critical care following elective repair of abdominal aortic aneurysm in four different institutions: *abstract* **355P**
Macrae WA Atlas of Common Pain Syndromes: *book review* **667**

Maddison V *see* Burn L **350P**
Mahadeva S, Cohen A and **Bellamy M** The stuck central venous catheter: beware of potential hazards **650**
Mahajan R *see* Stacey M **196P**; Moppett IK **196P**
Mahajan RP Clinical Anesthesia Practice: *book review* **664**
Mahajan RP *see* Moppett IK **204P**; Sherman RW **687**; Webster VL **265**
Mahfouf M *see* Kwok HF **206P**
Majedi PM *see* Orlikowski C **922**
Mak PHK and **Ooi RGB** Submental intubation *versus* tracheostomy. *correspondence* **344**
Makings EA, Beddow ECL, Wilkes M, Patel M, Hadley J, Benjamin N and **Hinds CJ** Decreased intragastric production of nitric oxide could predispose to ventilator-associated pneumonia: *abstract* **356P**
Makita K *see* Ishikawa S **605**
Maleck WH, Piper SN, Apfel CC and **Roewer N** Predictive models for postoperative nausea and vomiting: *correspondence* **339**
Malik M *see* Moppett IK **358P**
Mallet S *see* Marchant W **525**
Manara AR *see* Simpson TP **382**
Mapleson WW *see* Daoud Z **442**
Marchant W, Mallet S, Monte S and **Lyons G** Platelet function assessment in Glanzmann's thrombasthenia: *correspondence* **525**
Marchant WA and **Fox R** Postoperative use of a cough-assist device in avoiding prolonged intubation **644**
Marks C *see* Sutton P **366P**
Marshall JN *see* Wynne DM **659**
Marshall R *see* Olvera C **351P**
Martin RV, Smith P and **Pal SK** Correlation between theoretical toxic dose of a mixture of local anaesthetics and complication rate in patients undergoing brachial plexus block: a prospective analysis of 571 cases *abstract* **675P**
Martyn JAJ, Chang Y, Goudsouzian NG and **Patel SS** Pharmacodynamics of mivacurium chloride in 13- to 18-yr-old adolescents with thermal injury **580**
Marx G *see* McCrossan L **194P**
Maslowski P *see* Watt P **680P**
Mathew M and **Pal SK** Is A2 flag a predictor of mortality in burns patients: *abstract* **198P**
Matsumoto S *see* Asai T **670P**
Maze M *see* Ma D **739**
McAuley DF *see* Perkins GD **360P**; Sutton P **366P**
McBride WT *see* Allen SJ **195P**; Bedi A **546**
McCaul C, Tobin É, Boylan JF and **McShane AJ** Atracurium is associated with postoperative residual curarization **766**
McClelland AM *see* McNamee DA **702**
McClelland DB *see* McLellan S **197P**; McLellan S **197P**
McClelland DBL *see* McLellan SA **537**
McCrossan L, Marx G, Cope T, Swaraj S, Cowan C, Mostafa SM, Wenstone R and **Leuwer M** Stroke volume variation: a cardiac preload parameter in mechanically ventilated patients with severe sepsis?: *abstract* **194P**
McHugh GA *see* Thoms GMM **917**
McKeown DW *see* Graham CA **659**
McLellan S, Walsh TS, McClelland DB, Prowse CV and **Ross JA** The development of a flow cytometric technique for tracking transfused allogeneic red blood cells: *abstract* **197P**
McLellan S, Walsh TS, McClelland DB, Prowse CV, Millar AM and **Patel D** The survival of transfused red blood cells in critically ill patients *abstract* **197P**
McLellan SA, Walsh TS and **McClelland DBL** Should we demand fresh red blood cells for perioperative and critically ill patients?: *editorial* **537**
McMurray TJ *see* Allen SJ **195P**
McNamee DA, McClelland AM, Scott S, Milligan KR, Westman L and **Gustafsson U** Spinal anaesthesia: comparison of plain ropivacaine 5 mg ml^{-1} with bupivacaine 5 mg ml^{-1} for major orthopaedic surgery **702**
McNarry A and **Goldhill DR** When is a patient too sick for ICU admission? A case report and database analysis *abstract* **357P**
McNarry A *see* Goldhill DR **356P**
McShane AJ *see* McCaul C **766**
Mecklenburgh JS *see* Chawathe MS **672P**
Memmo A *see* Droghetti L **775**
Menda F *see* Senturk M **849**
Menigaux C, Guignard B, Adam F, Sessler DI, Joly V and **Chauvin M** Esmolol prevents movement and attenuates the BIS response to orotracheal intubation **857**
Menon G *see* Srikiran R **660**
Mergoni P *see* Paqueron X **697**
Mettam IM *see* Olufolabi AJ **652**
Michalek-Sauberer A *see* Sator-Katzenschlager S **764**
Millar AM *see* McLellan S **197P**
Miller K *see* Moppett IK **204P**
Miller KW The nature of sites of general anaesthetic action **17**
Miller KW, Richards CD, Roth SH and **Urban BW** Molecular and basic mechanisms of anaesthesia: *editorial* **1**
Miller NE *see* Peters CJ **361P**
Milligan KR *see* McNamee DA **702**
Millo J, Campbell K, Robson D, Salmon J and **Pigott D** Perioperative fluid management and the incidence of acute renal failure following coronary artery bypass surgery: *abstract* **358P**
Mills GH *see* Kwok HF **206P**; Schummer W **335**; Turnbull D **205P**
Miranda C *see* Walsh SJ **799**
Moganasundram S *see* Roberts RG **796**
Monte S *see* Marchant W **525**
Montigon O *see* Julien-Dolbec C **287**
Moons KGM *see* van Klei WA **221**
Moore CS, Wildsmith JAW and **Sheppard DE** Thigh rotation and the anterior approach to the sciatic nerve, an MRI study. *abstract* **676P**
Moppett I *see* Stacey M **196P**
Moppett IK, Gornall CB, Hancock SM and **Mahajan RP** Factors affecting the siphon effect in simulated cerebral circulation using a bench model: *abstract* **196P**
Moppett IK, Malik M and **Baxendale BR** Transoesophageal Doppler measurements are tolerable and reproducible in awake, ambulatory volunteers: *abstract* **358P**
Moppett IK, Miller K, Davies JA, Baxendale BR and **Mahajan RP** the effects of dopexamine on cerebral carbon dioxide reactivity: *abstract* **204P**
Morf D *see* Heidegger T **863**
Morgan P *see* Roberts RG **796**
Morgan-Hughes NJ *see* Schummer W **335**
Mori T *see* Karasawa F **271**
Morimoto Y *see* Shibano T **301**
Morin AM *see* Eberhart LHJ **760**
Morisaki H *see* Serita R **896**
Morita Y *see* Serita R **896**
Morley A *see* Krovvidi H **343**
Morris E *see* Naik P **359P**
Morris S *see* Jeffs SA **424**
Mostafa SM *see* McCrossan L **194P**
Mouton C *see* Forestier F **715**
Mueller CR *see* Girard T **571**
Müller M, Junger A, Bräu M, Kwapisz MM, Schindler E, Akintürk H, Benson M and **Hempelmann G** Incidence and risk calculation of inotropic support in patients undergoing cardiac surgery with cardiopulmonary bypass using an automated anaesthesia record-keeping system **398**
Murray JM *see* Bedi A **546**
Murthy BVS Anaesthesia OSCE. 2nd Edition *book review* **532**

Naik P, Morris E, Mackinnon S and **Singer M** Do critically ill patients with haematological malignancy survive intensive care and beyond? *abstract* **359P**
Nanjee MN *see* Peters CJ **361P**
Nargues N *see* Cannesson M **925**
Nash HA *In vivo* genetics of anaesthetic action **143**
Neilson J *see* Cooper GM **369**
Nel MR *see* Brunner MD **325**
Newnam PTF and **Watts JC** Mobile operating theatre. Why must it be mobile?: *correspondence* **187**
Newton DEF *see* Brunner MD **325**
Ng KFJ *see* Innerhofer P **934**
Ng A and **Smith G** Intraperitoneal administration of analgesia: is this practice of any utility?. *editorial* **535**
Ngan Kee WD, Shaw KS, Ma KC, Wong ASY and **Lee BB** Randomized, double-blind comparison of different inspired oxygen fractions during general anaesthesia for Caesarean section **556**

Nicholson G, **Pereira AC** and **Hall GM** Parkinson's disease and anaesthesia **904**
Nieminen K, **Westerèn-Punnonen S**, **Kokki H**, **Yppärilä H**, **Hyvärinen A** and **Partanen J** Sevoflurane anaesthesia in children after induction of anaesthesia with midazolam and thiopental does not cause epileptiform EEG **853**
Nightingale P Oxford Handbook of Anaesthesia: *book review* **346**
Nightingale P *see* Jones AG **526**
Nimmo AF *see* Banerjee TP **673P**
Norris A *see* Hinchliffe D **328**
Norris AM *see* O'Leary M **937**
Nuebling M *see* Heidegger T **863**

O'Leary M, **Dunsire MF**, **Norris AM** and **Hinchliffe D** Management of failed intubation in a septic parturient *correspondence* **937**
O'Neil MJ, **Brimacombe J**, **Richardson C**, **Keller C** and **Donald S** Mechanical closure of the vocal cords with the LMA ProSeal™: *correspondence* **936**
Oberling P *see* Pain L **614**
Oczenski W *see* Krenn H **637**
Okuda T *see* Karasawa F **271**
Oliver CD and **White SA** Unexplained fitting in three parturients suffering from postdural puncture headache **782**
Olufolabi AJ, **Charlton GA**, **Allen SA**, **Mettam IM** and **Roberts PR** Use of implantable cardioverter defibrillator and anti-arrhythmic agents in a parturient **652**
Olvera C, **Webb S**, **Phelps S**, **Batson S**, **Puddicome A**, **Marshall R** and **Bellingan GJ** Early hypoxaemia is a marker of outcome for pulmonary but not extrapulmonary acute respiratory distress syndrome: *abstract* **351P**
Ooi L *see* Jerman JC **882**
Ooi RGB *see* Mak PHK **344**
Oram M *see* Rousseau GF **846**
Orliaguet G *see* Bouhemad B **479**
Orlikowski C, **Majedi PM** and **Keil AD** Bacterial contamination of epidural needles after multiple skin passes **922**
Oshima T *see* Karasawa F **271**
Ovize M *see* Piriou V **486**
Owen D *see* Jerman JC **882**
Özatamer O *see* Sayin MM **242**
Ozkan T *see* Senturk M **849**

Pain L, **Launoy A**, **Fouquet N** and **Oberling P** Mechanisms of action of midazolam on expression of contextual fear in rats **614**
Pal SK *see* Martin RV **675P**; Mathew M **198P**; Sampathkumar S **202P**
Pallett E *see* Watt P **680P**
Paqueron X, **Lumbroso A**, **Mergoni P**, **Aubrun F**, **Langeron O**, **Coriat P** and **Riou B** Is morphine-induced sedation synonymous with analgesia during intravenous morphine titration? **697**
Park G *see* Coomber S **873**
Park GR *see* Burbridge K **359P**; Burbridge K **360P**
Partanen J *see* Nieminen K **853**
Patel A *see* Williams DG **839**
Patel A, **Randhawa N**, **Semenov RA** and **Bourgain JL** Transtracheal high frequency jet ventilation and iatrogenic injury: *correspondence* **184**
Patel D *see* McLellan S **197P**
Patel M *see* Makings EA **356P**
Patel N *see* Rao MP **363P**
Patel N, **Fernando R** and **Sodhi V** Urgency of Caesarean section, time to delivery and fetal outcome: a prospective observational study *abstract* **679P**
Patel SS *see* Martyn JAJ **580**
Patil V, **Barker GL**, **Harwood RJ** and **Woodall NM** Training course in local anaesthesia of the airway and fibreoptic intubation using course delegates as subjects **586**
Paton JFR *see* Pickering AE **207P**
Paw HGW Bilateral pleural effusions unexpected complication after left internal jugular venous catheterization for total parenteral nutrition **647**
Payen JF *see* Julien-Dolbec C **287**
Peine L *see* Eikermann M **277**
Pembeci K *see* Senturk M **849**
Pennefather S *see* Kendall J **203P**
Pennefather SH Cardiac Arrhythmias. Practical Notes on Interpretation and Treatment: *book review* **532**
Pennefather SH *see* Seymour AH **661**
Pentyala SN *see* Rebecchi MJ **62**
Pereira AC *see* Nicholson G **904**
Perel A *see* Berkenstadt H **509**
Perkins GD, **Giles S**, **McAuley DF**, **Routeledge H** and **Gao F** The influence of hydrogen ion concentration and haemoglobin concentration on the accuracy of the pulse oximeter (<SpO2>) *abstract* **360P**
Perkins GD, **Roberts C** and **Gao F** Delays in defibrillation· influence of different monitoring techniques **405**
Perner A *see* Due V **919**
Perrigault PF *see* Ryckwaert F **599**
Peters CJ, **Nanjee MN**, **Gordon AC**, **Miller NE** and **Hinds CJ** Proinflammatory modifications of lipoprotein structure and function in patients with septic shock: relationship to outcome *abstract* **361P**
Peters J *see* Eikermann M **277**
Petersen-Felix S *see* Luginbuhl M **389**
Phelps S *see* Olvera C **351P**
Phillips JMG, **Stedeford JC**, **Hartsilver E** and **Roberts C** Epidural abscess complicating insertion of epidural catheters **778**
Pickard S and **Goodman NW** How to Survive in Anaesthesia· *book review* **804**
Pickering AE, **Waki H**, **Headley PM** and **Paton JFR** Investigation of systemic bupivacaine toxicity using the *in situ* perfused working heart-brainstem preparation of the rat *abstract* **207P**
Pigott D *see* Millo J **358P**
Pilcher DV *see* David AC **938**
Pilcher DV, **Hamid S**, **Williams AJ** and **Davidson AC** Outcomes, cost, and long-term survival of patients referred to regional centre for weaning from mechanical ventilation: *abstract* **361P**
Pilcher DV, **Hamid S**, **Williams AJ** and **Davidson AC** The influence of diagnosis on survival and success in weaning patients from prolonged mechanical ventilation *abstract* **362P**
Pinaud M *see* Lejus C **693**
Piper SN *see* Maleck WH **339**
Piriou V, **Chiari P**, **Lhuillier F**, **Bastien O**, **Loufoua J**, **Raisky O**, **David JS**, **Ovize M** and **Lehot JJ** Pharmacological preconditioning comparison of desflurane, sevoflurane, isoflurane and halothane in rabbit myocardium **486**
Power I Manual of Pain Management: *book review* **666**
Poxon I *see* Allsop P **349P**
Prasad CV and **Drummond GB** Inadequate tidal volumes during biphasic pressure ventilation, caused by expiratory muscle contraction *abstract* **209P**
Priebe HJ Pulse Oximetry: *book review* **802**
Prince J *see* Allsop P **349P**
Priston M *see* Rousseau GF **846**
Prout J *see* Rao MP **363P**
Prowse CV *see* McLellan S **197P**, McLellan S **197P**
Puddicome A *see* Olvera C **351P**

Radke PW *see* Janssens U **237**
Räihä E *see* Ala-Kokko TI **438**
Raisky O *see* Piriou V **486**
Raj N *see* Wilkes AR **670P**
Raj N, **Henderson KA**, **Hall JE**, **Williams B** and **Harmer M** Evaluation of personal, environmental and biological exposure of paediatric anaesthetists to sevoflurane: *abstract* **675P**
Randhawa N *see* Patel A **184**
Rangasami J *see* Skinner CM **792**
Rao MP, **Jones JP**, **Lambert B** and **Krishnamurthy A** The influence of cell saver on transfusion requirements during elective abdominal aortic aneurysm repair: *abstract* **362P**
Rao MP, **Tote S**, **Patel N**, **Stephens R**, **Prout J** and **Shaw S** Use of central venous catheters in intensive care *abstract* **363P**
Rao SHG and **Scott NB** Pain and injury from epidural injection *correspondence* **188**
Rebecchi MJ and **Pentyala SN** Anaesthetic actions on other targets protein Kinase C and guanine nucleotide-binding proteins **62**
Reichlin F *see* Luginbühl M **389**
Renaudin M *see* Lejus C **693**
Reutenauer H *see* Julien-Dolbec C **287**
Rheineck-Leyssius AT *see* van Klei WA **221**

Richards CD Anaesthetic modulation of synaptic transmission in the mammalian CNS **79**
Richards CD *see* Miller KW **1**
Richards MJ, Lockey DJ and **Helm M** Quality of pre-hospital emergency ventilation in patients with severe head injury· *correspondence* **936**
Richardson C *see* O'Neil MJ **936**
Richardson J Practical Pain Management *book review* **666**
Ridley S *see* Jones AG **526**
Ridley S, Nightingale P, Jones AG and **Harper SJ** Ventilating in recovery—the way forward intensive therapy or critical care?: *correspondence* **526**
Riley B *see* Brooks A **351P**
Riou B *see* Beloeil H **567**; Bouhemad B **479**; Paqueron X **697**
Robb JD, Dakin J, Evans TW and **Cordingley JJ** Factors associated with intensive care outcome in patients with severe chronic respiratory disease· *abstract* **352P**
Roberts C *see* Perkins GD **405**; Phillips JMG **778**
Roberts H, Eddleston J and **Conway D** The effects of immunonutrition on clinical outcome in the critically ill. *abstract* **363P**
Roberts N *see* Dolling M **680P**
Roberts PR *see* Olufolabi AJ **652**
Roberts RG, Stallard NJ, Morgan P and **Moganasundram S** Recruitment manoeuvres on high frequency oscillation ventilation: *correspondence* **796**
Roberts SA Cuffed Portex tracheal tube *correspondence* **187**
Robertshaw HJ and **Brennan FM** TNFα cleaving enzyme (TACE) activity assessed by TIMP-s binding: *abstract* **676P**
Robson D *see* Millo J **358P**
Rodrigo N The confidential enquiries into maternal deaths in the UK (CEMD)—a 'sub-standard' report?: *correspondence* **528**
Roewer N *see* Maleck WH **339**
Romney M *see* Loughnan BA **466**
Roscoe A *see* Watt P **680P**
Ross JA and **Tunstall ME** Simulated use of premixed 0.25% isoflurane in 50% nitrous oxide and 50% oxygen **820**
Ross JA *see* McLellan S **197P**; Tunstall ME **814**
Rostami-Hodjegan A *see* Johnson TN **428**
Roth SH *see* Miller KW **1**
Rouet R *see* Yvon A **888**
Rousseau GF, Oram M, Barrington J, Priston M and **Swart M** Plasma lidocaine concentrations following insertion of 2% lidocaine gel into the uterine cavity after uterine balloon thermal ablation **846**
Routeledge H *see* Perkins GD **360P**
Rowan K *see* Stenhouse C **364P**
Rowbotham DJ *see* Schupp M **678P**; Watt P **680P**
Rowlands CA *see* Simpson TP **382**
Rowney DA *see* Brohi FA **525**
Rudge C *see* Burbridge K **359P**; Burbridge K **360P**
Rundshagen I, Schnabel K and **Schulte am Esch J** Impaired explicit memory after recovery from propofol/sufentanil anaesthesia is related to changes in the midlatency auditory evoked response **376**
Russell G *see* Kendall J **203P**
Russell GN *see* Seymour AH **661**
Russell WC *see* Francis S **517**
Rutherford P *see* Subbe CP **365P**; Subbe CP **365P**
Rutten CLG *see* van Klei WA **221**
Ruttmann TG, James MFM and **Finlayson J** Effects on coagulation of intravenous crystalloid or colloid in patients undergoing peripheral vascular surgery **226**
Ryckwaert F, Colson P, André E, Perrigault PF, Guillon G and **Barberis C** Haemodynamic effects of an angiotensin-converting enzyme inhibitor and angiotensin receptor antagonist during hypovolaemia in the anaesthetized pig **599**

Sadhasivam S *see* Sennaraj B **473**
Saenko EL *see* Dornan RIP **524**
Sainsbury M *see* Edge CJ **788**
Sakarya M *see* Troprak V **655**
Salmon J *see* Millo J **358P**
Sampathkumar S, Than M, Fenton R, Pal SK, Lockwood GG and **White DC** Attempting to estimate the rate of perfusion of the cerebral site of action of sevoflurane (2). *abstract* **202P**
Sanders JC Paediatric regional anaesthesia, a survey of practice in the United Kingdom **707**
Sandhu NS and **Capan LM** Ultrasound-guided infraclavicular brachial plexus block **254**
Sankar D and **Kini KJ** Respiratory monitoring of non-intubated patients using the 'PIPPA' breathing monitor *abstract* **677P**
Satoh M, Hirabayashi Y and **Seo N** Spontaneous breathing combined with high frequency ventilation during bronchoscopic resection of a large tracheal tumour **641**
Satoh T *see* Serita R **896**
Sator-Katzenschlager S, Deusch E, Dolezal S, Michalek-Sauberer A, Grubmüller R, Heinze G and **Wedrich A** Sevoflurane and propofol decrease intraocular pressure equally during non-ophthalmic surgery and recovery **764**
Savage R, Håkanson E, Konstantinov I, Fransson SG and **Svedjeholm R** Prone, head down for pulmonary haemorrhage: *correspondence* **185**
Sayin MM, Özatamer O, Ta□_öz R, Kilinç K and **Ünal N** Propofol attenuates myocardial lipid peroxidation during coronary artery bypass grafting surgery **242**
Schellhaass A *see* Boldt J **722**
Schiffer E *see* Garnerin P **633**
Schindler E *see* Muller M **398**
Schnabel K *see* Rundshagen I **376**
Scholz A Mechanisms of (local) anaesthetics on voltage-gated sodium and other ion channels **52**
Schreiber SJ, Lambert UKW, Doepp F and **Valdueza JM** Effects of prolonged head-down tilt on internal jugular vein cross-sectional area **769**
Schubert C *see* Heidegger T **863**
Schulte am Esch J *see* Rundshagen I **376**
Schummer C *see* Schummer W **335**
Schummer W, Schummer C, Fuchs J, Voigt R, Morgan-Hughes NJ, Turnbull D and **Mills GH** Sudden upper airway obstruction due to invisible rain-out in the heat and moisture exchange filter. *correspondence* **335**
Schupp M, Hall NA, Sharpe P and **Rowbotham DJ** Actigraphic measurements of sleep variables and circadian rhythm in chronic pain patients compared with healthy controls· *abstract* **678P**
Schwarzbauer C *see* Heinke W **112**
Scott NB *see* Rao SHG **188**
Scott S *see* McNamee DA **702**
Sear JW *see* Sewell JC **672P**
Sedgwick PM *see* Brill S **711**
Semenov RA *see* Patel A **184**
Sennaraj B, Shende D, Sadhasivam S, Ilavajady S and **Jagan D** Management of post-strabismus nausea and vomiting in children using ondansetron· a value-based comparison of outcomes **473**
Senturk M, Pembeci K, Menda F, Ozkan T, Gucyetmez B, Tugrul M, Cami E and **Akpir K** Effects of intramuscular administration of lidocaine or bupivacaine on induction and maintenance doses of propofol evaluated by bispectral index **849**
Seo N *see* Satoh M **641**
Serita R, Morisaki H, Ai K, Morita Y, Innami Y, Satoh T, Kosugi S, Kotake Y and **Takeda J** Sevoflurane preconditions stunned myocardium in septic but not healthy isolated rat hearts **896**
Serpell MG, Fettes PDW and **Wildsmith JAW** Pencil point spinal needles and neurological damage. *correspondence* **800**
Sessler DI *see* Menigaux C **857**
Sewell JC and **Sear JW** A preliminary CoMFA model for chemically diverse intravenous general anaesthetics· *abstract* **672P**
Seymour AH, Lynch L, Pennefather SH and **Russell GN** An audit of Robertshaw double lumen tube placement using the fibreoptic bronchoscope: *correspondence* **661**
Shah JL Epidural test dose with an 'eye on the end of the catheter': *abstract* **207P**
Shankar R, Fettes PDW and **Wildsmith JAW** Somebody else's nervous system *correspondence* **662**
Shapiro WA *see* Stefanutto TB **527**
Sharpe P *see* Schupp M **678P**; Dolling M **678P**; Dolling M **680P**
Sharrock NE *see* Holte K **622**
Shaw S *see* Rao MP **363P**
Shelly MP *see* Clayton JA **191**
Shende D *see* Sennaraj B **473**

Sheppard DE *see* Moore CS **676P**
Sherman RW, Bowie RA, Henfrey MME, Mahajan RP and **Bogod D** Cerebral haemodynamics in pregnancy and pre-eclampsia as assessed by transcranial Doppler ultrasonography **687**
Sherwood N *see* Hack H **797**; Kannan S **512**
Shibano T, Morimoto Y, Kemmotsu O, Shikama H, Hisano K and **Hua Y** Effects of mild and moderate hypothermia on apoptosis in neuronal PC12 cells **301**
Shikama H *see* Shibano T **301**
Shingu K *see* Asai T **670P**
Shore S *see* Coomber S **873**
Sieber T *see* Heidegger T **863**
Siemers M *see* Detsch O **294**
Sigurdsson GH *see* Luginbuhl M **389**
Simpson TP, Manara AR, Kane NM, Barton RL, Rowlands CA and **Butler SR** Effect of propofol anaesthesia on the event-related potential mismatch negativity and the auditory-evoked potential N1 **382**
Singer M *see* Coluzzi F **352P**; Hails J **354P**; Naik P **359P**
Skinner CM and **Rangasami J** Preoperative use of herbal medicines: a patient survey **792**
Slater RM *see* Wasson CMA **367P**
Smart D *see* Jerman JC **882**
Smart NG, Varveris DA and **Jacobs P** Use of the Intubating Laryngeal Mask in failed intubation associated with amyloid macroglossia: *correspondence* **186**
Smith G *see* Ng A **535**
Smith M Anesthesia and Neurosurgery: *book review* **189**
Smith P *see* Martin RV **675P**
Smurthwaite GJ *see* Hariprasad M **927**
Sodhi V *see* Patel N **679P**
Soni N Critical Care Medicine: Principles of Diagnosis and Management in the Adult: *book review* **190**
Spahn DR Problems in Anesthesia. Cardiothoracic Surgery: *book review* **347**
Spahn DR *see* Chassot PG **747**
Spittle CSN *see* Beavis SE **350P**
Srikiran R and **Menon G** Prediction of neurological outcome following outside hospital cardio-respiratory arrest: *correspondence* **660**
Stables RH *see* Aziz S **665**
Stacey M, Moppett I, Athanassiou L and **Mahajan R** The effect of systemic compliance on the non-invasive assessment of zero-flow pressure in a bench model of pulsatile flow: *abstract* **196P**
Stacey R *see* Edge CJ **514**
Stallard NJ *see* Roberts RG **796**
Stedeford JC *see* Phillips JMG **778**
Stefanutto TB, Shapiro WA and **Wright PMC** Anaphylactic reaction to isosulphan blue: *correspondence* **527**
Stegen B *see* Eikermann M **277**
Stenhouse C, Hanks R, Goldfrad C and **Rowan K** Let's reach out for outreach in critical care: *abstract* **364P**
Stenhouse CW *see* Allsop P **349P**; Gopal S **364P**
Stephens R *see* Rao MP **363P**
Stern M *see* Dalibon N **930**
Stott SA *see* Cuthbertson BH **247**
Streif W *see* Innerhofer P **934**
Stubbins K *see* Dobbs P **353P**, Dobbs P **353P**
Subbe CP, Falcus J, Rutherford P and **Gemmel L** Early warning scores and duration of hospital stay: *abstract* **365P**
Subbe CP, Williams L, Davies R, Rutherford P and **Gemmel L** Dilemmas with early warning scores: *abstract* **365P**
Subramaniam R and **Atallah F** Retroperitoneoscopic excision of phaeochromocytoma: *correspondence* **188**
Sudheer PS, Ateleanu B, Hall JE, Logan SW and **Harmer M** Haemodynamic effects of the prone position for spinal surgery: TIVA versus inhalation anaesthesia: *abstract* **674P**
Suttner S *see* Boldt J **722**
Sutton P, Marks C, Giles S, McAuley D and **Gao F** Why change a patient's ventilator system? A comparison of continuous positive airway pressure (CPAP) through the Galileo ventilator *vs* a Drager CF800 device: *abstract* **366P**
Svedjeholm R *see* Savage R **185**
Swaraj S *see* McCrossan L **194P**
Swart M *see* Rousseau GF **846**
Sweeney BP Why does smoking protect against PONV? *editorial* **810**
Symonds RP *see* Appadurai IR **342**
Syndercombe A *see* Zimmer CR **203P**

Takeda J *see* Serita R **896**
Tanner MS *see* Johnson TN **428**
Tansey PJ *see* Howie JC **214**
Tasöz R *see* Sayin MM **242**
Telci L, Esen F, Akcora D, Erden T, Canbolat AT and **Akpir K** Evaluation of effects of magnesium sulphate in reducing intraoperative anaesthetic requirements **594**
Terrien X *see* Yvon A **888**
Than M *see* Sampathkumar S **202P**
Thomas GL and **Columb MO** Basic Statistics and Epidemiology A Practical Guide: *book review* **943**
Thomas M *see* Gould TH **446**
Thomas TA and **Cooper GM** Maternal deaths from anaesthesia An extract from *Why Mothers Die 1997–1999*, the Confidential Enquiries into Maternal Deaths in the United Kingdom **499**
Thompson JP *see* Francis S **517**; Watt P **680P**
Thoms GMM, HcHugh GA and **Lack JA** What information do anaesthetists provide for patients? **917**
Thomson DA *see* Wahl A **519**
Thorne G *see* Gould TH **446**
Thornton C *see* Brunner MD **325**
Tiplady B *see* Drummond GB **200P**
Tivey M *see* Allsop P **349P**
Tivey M, Harris P, West M, Carr J, Coates SJ, Cunningham MJ and **Allsop P** Time course for internal jugular and subclavian central venous catheter tip colonization: *abstract* **349P**
Tobin É *see* McCaul C **766**
Todd C *see* Coomber S **873**
Toprak V, Yentur A and **Sakarya M** Anaesthetic management of severe bradycardia during general anaesthesia using temporary cardiac pacing **655**
Tote S *see* Rao MP **363P**
Tran J *see* Kendall J **203P**
Treves S *see* Girard T **571**
Tropres I *see* Julien-Dolbec C **287**
Trudell JR and **Bertaccini E** Molecular modelling of specific and non-specific anaesthetic interactions **32**
Tucker GT *see* Johnson TN **428**
Tugrul M *see* Senturk M **849**
Tunstall ME and **Ross JA** Phase behaviour of premixed 0 25% isoflurane in 50% nitrous oxide and 50% oxygen **814**
Tunstall ME *see* Ross JA **820**
Turnbull D *see* Schummer W **335**
Turnbull D, Barker A and **Mills GH** functional magnetic nerve stimulation of the abdominal muscles developmental of an artificial cough: *abstract* **205P**
Twigg SJ and **Cook TM** Anaesthesia in an adult with Rubenstein-Taybi syndrome using the ProSeal laryngeal mask airway **786**

Ünal N *see* Sayin MM **242**
Urban BW and **Bleckwenn M** Concepts and correlations relevant to general anaesthesia **3**
Urban BW Current assessment of targets and theories of anaesthesia **167**
Urban BW *see* Miller KW **1**
Urwyler A *see* Girard T **571**

Vahle-Hinz C and **Detsch O** What can *in vivo* electrophysiology in animal models tell us about mechanisms of anaesthesia? **123**
Vahle-Hinz C *see* Detsch O **294**
Valdueza JM *see* Schreiber SJ **769**
van der Vyver M, Halpern S and **Joseph G** Patient-controlled epidural analgesia *versus* continuous infusion for labour analgesia a meta-analysis **459**
Van Gessel E *see* Fournier R **562**; Garnerin P **633**
van Klei WA, Moons KGM, Rheineck-Leyssius AT, Kalkman CJ, Rutten CLG, Knape JTA and **Grobbee DE** Validation of a clinical prediction rule to reduce preoperative type and screen procedures **221**
Varin F *see* Laurin J **832**
Varveris DA *see* Smart NG **186**

Vaughan STA, MacKillop A, Fryer JM, Laurence AS and **Forshaw S** Fluid replacement during Picolax® bowel preparation: the consequences for anaesthesia: *abstract* **674P**
Voigt R *see* Schummer W **335**
Vollmer T *see* Genzwuerker HV **733**

Wahl A, Eberli FR, Thomson DA and **Luginbühl M** Coronary artery spasm and non-Q-wave myocardial infarction following intravenous ephedrine in two healthy women under spinal anaesthesia **519**
Waki H *see* Pickering AE **207P**
Waldmann C *see* Edge CJ **514**
Walker JD Posture used by anaesthetists during laryngoscopy **772**
Walker MB *see* Duxbury MS **366P**
Walsh EM and **Blanloeil Y** Methods of post-thoracotomy analgesia: *correspondence* **184**
Walsh SJ, Bedi A and **Miranda C** Successful defibrillation in the prone position: *correspondence* **799**
Walsh TS Critical Care Focus. Number 8· Blood and Blood Transfusion: *book review* **531**
Walsh TS *see* McLellan S **197P**; McLellan S **197P**; McLellan SA **537**
Wang YT *see* Ge SJ **260**
Wang ZD *see* Ge SJ **260**
Wasson CMA, Greer R, Dawson S and **Slater RM** An assessment of the temperature component of the early warning score *abstract* **367P**
Watson GW *see* Macnaughton PD **356P**
Watt JWH Pressure support ventilation and the critically ill patient with muscle weakness: *editorial* **373**
Watt JWH Spinal Cord Injury Pain· Assessment, Mechanisms, and Management *book review* **803**
Watt P, Williams J, Roscoe A, Pallett E, Maslowski P, Thompson JP and **Rowbotham D** Recording postoperative pain in ambulatory surgery· further evaluation of a revised electronic data collection device· *abstract* **680P**
Watts JC *see* Newnam PTF **187**
Webb S *see* Olvera C **351P**
Weber A *see* Fournier R **562**
Webster NR Inflammation and the coagulation system *editorial* **216**
Webster NR *see* Cuthbertson BH **247**; El Sakka NE **199P**; Engelhardt T **201P**; Engelhardt T **202P**; Engelhardt T **635**; Galley HF **198P**; Lowe PR **199P**
Webster VL and **Mahajan RP** Transient hyperaemic response to assess vascular reactivity of skin, effect of locally iontophoresed sodium nitroprusside **265**
Wedrich A *see* Sator-Katzenschlager S **764**
Weldon B *see* Halligan M **671P**
Wenstone R *see* McCrossan L **194P**
West M *see* Tivey M **349P**
Westerén-Punnonen S *see* Nieminen K **853**
Westman L *see* McNamee DA **702**
White DC *see* Sampathkumar S **202P**
White SA *see* Oliver CD **782**
White SM Chemical and biological weapons. Implications for anaesthesia and intensive care **306**
Wildsmith JAW *see* Moore CS **676P**; Serpell MG **800**; Shankar R **662**
Wilhelm S *see* Ma D **739**
Wilkes AR Comparison of two techniques for measuring penetration of sodium chloride particles through breathing system filters **541**
Wilkes AR, Hodzovic I and **Latto IP** Comparison of the peak forces that can be exerted by multiple-use and single-use bougies in vitro: *abstract* **671P**
Wilkes AR, Raj N and **Hall JE** Effect of repeated exposure on the incidence of adverse airway events during brief nasal inhalations of anaesthetics: *abstract* **670P**
Wilkes M *see* Makings EA **356P**
Wilkes RG *see* Cowan CM **452**
Williams AJ *see* Pilcher DV **361P**; Pilcher DV **362P**
Williams B *see* Raj N **675P**
Williams DG, Patel A and **Howard RF** The pharmacogenetics of codeine metabolism in an urban population of children and its implications for analgesic reliability **839**
Williams J *see* Watt P **680P**
Williams L *see* Subbe CP **365P**
Wilson APR *see* Hails J **354P**
Wong ASY *see* Ngan Kee WD **556**
Woodall NM *see* Patil V **586**
Worthmann F *see* Behnke H **251**
Wright PMC *see* Stefanutto TB **527**
Wulf H *see* Behnke H **251**; Eberhart LHJ **760**
Wynne DM and **Marshall JN** Risk of accidental extubation with disposable tonsillectomy instruments· *correspondence* **659**

Yentur A *see* Troprak V **655**
Yokoyama K *see* Ishikawa S **605**
Yppärilä H *see* Nieminen K **853**
Yvon A, Hanouz J-L, Terrien X, Ducouret P, Rouet R, Bricard H and **Gérard J-L** Electrophysiological effects of morphine in an *in vitro* model of the 'border zone' between normal and ischaemic–reperfused guinea-pig myocardium **888**

Zatelli R *see* Droghetti L **775**
Zbinden AM *see* Luginbuhl M **389**
Zhuang XL *see* Ge SJ **260**
Ziegler A *see* Julien-Dolbec C **287**
Zimmer CR, Syndercombe A, Edmondson L and **Duggan JE** Intragastric pressure in 100 paralysed surgical patients: *abstract* 203P
Zorzato F *see* Girard T **571**

British Journal of Anaesthesia 89 (6): 955–66 (2002)

VOLUME 89 • SUBJECT INDEX

acid–base equilibrium, acidosis, Lactic acidosis in the rectal lumen of patients with septic shock measured by luminal equilibrium dialysis **919**

agonists, adrenergic, Comparison of morphine alone with morphine plus clonidine for postoperative patient-controlled analgesia **424**

  Coronary artery spasm and non-Q-wave myocardial infarction following intravenous ephedrine in two healthy women under spinal anaesthesia **519**

agonists, beta-adrenergic, Shortage of isoproterenol (isoprenaline) hydrochloride: *correspondence* **528**

airway, Airway management in the emergency department: *correspondence* **659**

  Determining natural variation through eigenvector projections in the human airway: *abstract* **204P**

  Management of a known difficult airway in a morbidly obese patient with gross supraglottic oedema secondary to thyroid disease **927**

airway, difficult, Fibreoptic tracheal intubation after placement of the laryngeal tube **733**

airway, obstruction, Complete airway obstruction in a ventilated patient after oesophageal dilation **517**

  Spontaneous breathing combined with high frequency ventilation during bronchoscopic resection of a large tracheal tumour **641**

airway, patency, The effect of airway manoeuvres and route of respiration on spatial orientation of the upper airway: *abstract* **205P**

airway, reflexes, Postoperative use of a cough-assist device in avoiding prolonged intubation **644**

airway, technique, Mechanical closure of the vocal cords with the LMA ProSeal™: *correspondence* **936**

allergy, Anaphylactic reaction to isosulphan blue: *correspondence* **527**

  Probable allergic reaction to cyclosporin and early formation of thrombi on a pulmonary artery catheter: two unusual complications during bilateral lung transplantation **930**

anaesthesia, Atracurium is associated with postoperative residual curarization **766**

  Submental intubation *versus* tracheostomy: *correspondence* **344**

  Equipment problems during anaesthesia—are they a quality problem? **825**

  Is comparison of changes in cardiac output, assessed by different methods, better than only comparing cardiac output to the reference method?: *correspondence* **336**

  Molecular and basic mechanisms of anaesthesia: *editorial* **1**

  Parkinson's disease and anaesthesia **904**

  Pharmacokinetics of 0.75% ropivacaine and 0.5% bupivacaine after ilioinguinal-iliohypogastric nerve block in children **438**

  Phenotyping malignant hyperthermia susceptibility by measuring halothane-induced changes in myoplasmic calcium concentration in cultured human skeletal muscle cells **571**

  What can *in vivo* electrophysiology in animal models tell us about mechanisms of anaesthesia? **123**

anaesthesia, audit, Management of post-strabismus nausea and vomiting in children using ondansetron: a value-based comparison of outcomes **473**

  Patient satisfaction with anaesthesia care: development of a psychometric questionnaire and benchmarking among six hospitals in Switzerland and Austria **863**

anaesthesia, binding sites, The nature of sites of general anaesthetic action **17**

anaesthesia, depth, BIS—cautionary interpretation of data in children: *abstract* **672P**

  Changes in the rapidly extracted auditory evoked potentials index and the bispectral index during sedation induced by propofol or midazolam under epidural block **260**

  Comparison of ocular microtremor and bispectral index during sevoflurane anaesthesia **551**

  Concepts and correlations relevant to general anaesthesia **3**

  Current assessment of targets and theories of anaesthesia **167**

  Effect of propofol anaesthesia on the event-related potential mismatch negativity and the auditory-evoked potential N1 **382**

  Effect of a single dose of esmolol on the bispectral index scale (BIS) during propofol/fentanyl anaesthesia **509**

  Randomized, double-blind comparison of different inspired oxygen fractions during general anaesthesia for Caesarean section **556**

  Saliva cyclic GMP increases during anaesthesia **635**

anaesthesia, general, Anaesthetic modulation of synaptic transmission in the mammalian CNS **79**

  Concepts and correlations relevant to general anaesthesia **3**

  Confidential enquiries into maternal deaths, 1997–1999: *editorial* **369**

  Current assessment of targets and theories of anaesthesia **167**

  In vivo characterization of clinical anaesthesia and its components **156**

  Maternal deaths from anaesthesia. An extract from *Why Mothers Die 1997–1999*, the Confidential Enquiries into Maternal Deaths in the United Kingdom **499**

  Predictive models for postoperative nausea and vomiting: *correspondence* **339**

  Saliva cyclic GMP increases during anaesthesia **635**

  The confidential enquiries into maternal deaths in the UK (CEMD)—a 'sub-standard' report? *correspondence* **528**

  The effects of general anaesthetics on ligand-gated ion channels **41**

  The nature of sites of general anaesthetic action **17**

anaesthesia, obstetric, Confidential enquiries into maternal deaths, 1997–1999: *editorial* **369**

  Evaluation of S1 motor block to determine a safe, reliable test dose for epidural analgesia **442**

  Management of failed intubation in a septic parturient **328**

  Management of failed intubation in a septic parturient: *correspondence* **937**

  Maternal deaths from anaesthesia. An extract from *Why Mothers Die 1997–1999*, the Confidential Enquiries into Maternal Deaths in the United Kingdom **499**

  Randomized, double-blind comparison of different inspired oxygen fractions during general anaesthesia for Caesarean section **556**

  The confidential enquiries into maternal deaths in the UK (CEMD)—a 'sub-standard' report? *correspondence* **528**

  Unexplained fitting in three parturients suffering from postdural puncture headache **782**

  Urgency of Caesarean section, time to delivery and fetal outcome: a prospective observational study: *abstract* **679P**

  Use of implantable cardioverter defibrillator and anti-arrhythmic agents in a parturient **652**

anaesthesia, paediatric, Cerebrovascular carbon dioxide reactivity in children anaesthetized with sevoflurane: *correspondence* **525**

  Contribution of midazolam and its 1-hydroxy metabolite to preoperative sedation in children: a pharmacokinetic-pharmacodynamic analysis **428**

  Management of intraoperative pulmonary oedema in a child following systemic absorption of phenylephrine eyedrops: *correspondence* **343**

  Optimal rocuronium dose for intubation during inhalation induction with sevoflurane in children **277**

  Paediatric regional anaesthesia, a survey of practice in the United Kingdom **707**

anaesthesia, patient information, What information do anaesthetists provide for patients? **917**

anaesthesia, subarachnoid, Pencil point spinal needles and neurological damage: *correspondence* **800**

anaesthesia, urology, Air embolism diagnosis with single-photon emission tomography and successful hyperbaric oxygen therapy **775**

anaesthetic techniques, Intraperitoneal administration of analgesia: is this practice of any utility?: *editorial* **535**

anaesthetic techniques, anaesthetist posture, Posture used by anaesthetists during laryngoscopy **772**

anaesthetic techniques, combined subarachnoid epidural, Somebody else's nervous system: *correspondence* **662**

anaesthetic techniques, epidural, Bacterial contamination of epidural needles after multiple skin passes **922**

  Confidential enquiries into maternal deaths, 1997–1999: *editorial* **369**

© The Board of Management and Trustees of the British Journal of Anaesthesia

Effect of thoracic epidural anaesthesia on colonic blood flow **446**
Effectiveness of acute postoperative pain management: I Evidence from published data **409**
Epidural abscess complicating insertion of epidural catheters **778**
Epidural analgesia and backache: a randomized controlled comparison with intramuscular meperidine for analgesia during labour **466**
Epidural test dose with an 'eye on the end of the catheter': *abstract* **207P**
Evaluation of S1 motor block to determine a safe, reliable test dose for epidural analgesia **442**
Management of failed intubation in a septic parturient **328**
Management of failed intubation in a septic parturient: *correspondence* **937**
Maternal deaths from anaesthesia An extract from *Why Mothers Die 1997–1999*, the Confidential Enquiries into Maternal Deaths in the United Kingdom **499**
Paediatric regional anaesthesia, a survey of practice in the United Kingdom **707**
Pain and injury from epidural injection: *correspondence* **188**
Pharmacokinetics of 0.75% ropivacaine and 0 5% bupivacaine after ilioinguinal-iliohypogastric nerve block in children **438**
The confidential enquiries into maternal deaths in the UK (CEMD)—a 'sub-standard' report?: *correspondence* **528**
anaesthetic techniques, i.v., Effects of intramuscular administration of lidocaine or bupivacaine on induction and maintenance doses of propofol evaluated by bispectral index **849**
Esmolol prevents movement and attenuates the BIS response to orotracheal intubation **857**
Evaluation of effects of magnesium sulphate in reducing intraoperative anaesthetic requirements **594**
anaesthetic techniques, inhalation, Effect of repeated exposure on the incidence of adverse airway events during brief nasal inhalations of anaesthetics: *abstract* **670P**
Influence of fresh gas and circuit on induction of anaesthesia with sevoflurane: *abstract* **673P**
anaesthetic techniques, regional, Intrathecal morphine overdose during combined spinal–epidural block for Caesarean delivery **925**
Paediatric regional anaesthesia, a survey of practice in the United Kingdom **707**
Spinal anaesthesia: comparison of plain ropivacaine 5 $mg\,ml^{-1}$ with bupivacaine 5 $mg\,ml^{-1}$ for major orthopaedic surgery **702**
anaesthetic techniques, regional, brachial plexus, Correlation between theoretical toxic dose of a mixture of local anaesthetics and complication rate in patients undergoing brachial plexus block: a prospective analysis of 571 cases: *abstract* **675P**
Ultrasound-guided infraclavicular brachial plexus block **254**
anaesthetic techniques, regional, cervical plexus, Remifentanil or propofol for sedation during carotid endartectomy under cervical plexus block **637**
anaesthetic techniques, regional, intercostal, Plasma concentration of ropivacaine after intercostal blocks for video-assisted thoracic surgery **251**
anaesthetic techniques, regional, sciatic, Thigh rotation and the anterior approach to the sciatic nerve, an MRI study. *abstract* **676P**
anaesthetic techniques, subarachnoid, Spinal anaesthesia: comparison of plain ropivacaine 5 $mg\,ml^{-1}$ with bupivacaine 5 $mg\,ml^{-1}$ for major orthopaedic surgery **702**
anaesthetic techniques, test doses, Evaluation of S1 motor block to determine a safe, reliable test dose for epidural analgesia **442**
anaesthetics gases, Concepts and correlations relevant to general anaesthesia **3**
Current assessment of targets and theories of anaesthesia **167**
anaesthetics gases, nitrous oxide, Expansion of air bubbles in aqueous solutions of nitrous oxide or xenon **282**
Maintenance of stable cuff pressure in the Brandt™ tracheal tube during anaesthesia with nitrous oxide **271**
Neuroprotective and neurotoxic properties of the 'inert' gas, xenon **739**
Phase behaviour of premixed 0.25% isoflurane in 50% nitrous oxide and 50% oxygen **814**
Simulated use of premixed 0 25% isoflurane in 50% nitrous oxide and 50% oxygen **820**
anaesthetics gases, premixed gases, Phase behaviour of premixed 0.25% isoflurane in 50% nitrous oxide and 50% oxygen **814**
Simulated use of premixed 0.25% isoflurane in 50% nitrous oxide and 50% oxygen **820**
anaesthetics gases, xenon, Expansion of air bubbles in aqueous solutions of nitrous oxide or xenon **282**
Neuroprotective and neurotoxic properties of the 'inert' gas, xenon **739**
Xenon has no effect on cytokine balance and adhesion molecule expression within an isolated cardiopulmonary bypass system **546**
anaesthetics i.v., A preliminary CoMFA model for chemically diverse intravenous general anaesthetics. *abstract* **672P**
Current assessment of targets and theories of anaesthesia **167**
What can *in vivo* electrophysiology in animal models tell us about mechanisms of anaesthesia? **123**
anaesthetics i.v., ketamine, Neuroprotective and neurotoxic properties of the 'inert' gas, xenon **739**
anaesthetics i.v., propofol, Auditory evoked response during propofol anaesthesia after pre-induction with midazolam **325**
Changes in the rapidly extracted auditory evoked potentials index and the bispectral index during sedation induced by propofol or midazolam under epidural block **260**
Concepts and correlations relevant to general anaesthesia **3**
Effect of a single dose of esmolol on the bispectral index scale (BIS) during propofol/fentanyl anaesthesia **509**
Effect of propofol anaesthesia on the event-related potential mismatch negativity and the auditory-evoked potential N1 **382**
Impaired explicit memory after recovery from propofol/sufentanil anaesthesia is related to changes in the midlatency auditory evoked response **376**
Propofol attenuates myocardial lipid peroxidation during coronary artery bypass grafting surgery **242**
Remifentanil or propofol for sedation during carotid endartectomy under cervical plexus block **637**
Role of propofol and its solvent, intralipid, in nitric oxide-induced peripheral vasodilatation in dogs **492**
Sevoflurane and propofol decrease intraocular pressure equally during non-ophthalmic surgery and recovery **764**
Spontaneous breathing combined with high frequency ventilation during bronchoscopic resection of a large tracheal tumour **641**
The output of two sevoflorane vaporizers in the presence of helium. *correspondence* **797**
anaesthetics i.v., thiopental, Sevoflurane anaesthesia in children after induction of anaesthesia with midazolam and thiopental does not cause epileptiform EEG **853**
anaesthetics local, Analgesia for pelvic brachytherapy· *correspondence* **342**
Correlation between theoretical toxic dose of a mixture of local anaesthetics and complication rate in patients undergoing brachial plexus block: a prospective analysis of 571 cases: *abstract* **675P**
Effects of intramuscular administration of lidocaine or bupivacaine on induction and maintenance doses of propofol evaluated by bispectral index **849**
Mechanisms of (local) anaesthetics on voltage-gated sodium and other ion channels **52**
anaesthetics local, bupivacaine, Evaluation of S1 motor block to determine a safe, reliable test dose for epidural analgesia **442**
Investigation of systemic bupivacaine toxicity using the *in situ* perfused working heart-brainstem preparation of the rat: *abstract* **207P**
Pharmacokinetics of 0.75% ropivacaine and 0.5% bupivacaine after ilioinguinal-iliohypogastric nerve block in children **438**
Spinal anaesthesia: comparison of plain ropivacaine 5 $mg\,ml^{-1}$ with bupivacaine 5 $mg\,ml^{-1}$ for major orthopaedic surgery **702**
anaesthetics local, levobupivacaine, Safer labelling of levobupivacaine· *correspondence* **345**
anaesthetics local, lidocaine, Plasma lidocaine concentrations following insertion of 2% lidocaine gel into the uterine cavity after uterine balloon thermal ablation **846**
Ultrasound-guided infraclavicular brachial plexus block **254**
anaesthetics local, ropivacaine, Pharmacokinetics of 0 75% ropivacaine and 0.5% bupivacaine after ilioinguinal-iliohypogastric nerve block in children **438**
Plasma concentration of ropivacaine after intercostal blocks for video-assisted thoracic surgery **251**
Spinal anaesthesia: comparison of plain ropivacaine 5 $mg\,ml^{-1}$ with bupivacaine 5 $mg\,ml^{-1}$ for major orthopaedic surgery **702**

anaesthetics volatile, Current assessment of targets and theories of anaesthesia **167**
Differential effects of isoflurane on excitatory and inhibitory synaptic inputs to thalamic neurones *in vivo* **294**
In vivo genetics of anaesthetic action **143**
Pharmacological preconditioning: comparison of desflurane, sevoflurane, isoflurane and halothane in rabbit myocardium **486**
What can *in vivo* electrophysiology in animal models tell us about mechanisms of anaesthesia? **123**
anaesthetics volatile, atmospheric pollution, Evaluation of personal, environmental and biological exposure of paediatric anaesthetists to sevoflurane: *abstract* **675P**
anaesthetics volatile, desflurane, Concepts and correlations relevant to general anaesthesia **3**
anaesthetics volatile, diethyl ether, Concepts and correlations relevant to general anaesthesia **3**
anaesthetics volatile, halothane, Effects of halothane and isoflurane on the contraction, relaxation and energetics of rat diaphragmatic muscle **479**
Phenotyping malignant hyperthermia susceptibility by measuring halothane-induced changes in myoplasmic calcium concentration in cultured human skeletal muscle cells **571**
anaesthetics volatile, isoflurane, Concepts and correlations relevant to general anaesthesia **3**
Effects of halothane and isoflurane on the contraction, relaxation and energetics of rat diaphragmatic muscle **479**
Phase behaviour of premixed 0.25% isoflurane in 50% nitrous oxide and 50% oxygen **814**
Simulated use of premixed 0.25% isoflurane in 50% nitrous oxide and 50% oxygen **820**
anaesthetics volatile, sevoflurane, Sevoflurane preconditions stunned myocardium in septic but not healthy isolated rat hearts **896**
Attempting to estimate the rate of perfusion of the cerebral site of action of sevoflurane (2): *abstract* **202P**
Cerebrovascular carbon dioxide reactivity in children anaesthetized with sevoflurane: *correspondence* **525**
Comparison of ocular microtremor and bispectral index during sevoflurane anaesthesia **551**
Concepts and correlations relevant to general anaesthesia **3**
Evaluation of personal, environmental and biological exposure of paediatric anaesthetists to sevoflurane. *abstract* **675P**
Fluoride excretion in children after sevoflurane anaesthesia **693**
Randomized, double-blind comparison of different inspired oxygen fractions during general anaesthesia for Caesarean section **556**
Sevoflurane anaesthesia in children after induction of anaesthesia with midazolam and thiopental does not cause epileptiform EEG **853**
Sevoflurane and propofol decrease intraocular pressure equally during non-ophthalmic surgery and recovery **764**
anaesthetics, molecular targets, Anaesthetic actions on other targets. protein kinase C and guanine nucleotide-binding proteins **62**
analgesia, Analgesia for pelvic brachytherapy *correspondence* **342**
Current assessment of targets and theories of anaesthesia **167**
Intraperitoneal administration of analgesia: is this practice of any utility? *editorial* **535**
Is morphine-induced sedation synonymous with analgesia during intravenous morphine titration? **697**
What can *in vivo* electrophysiology in animal models tell us about mechanisms of anaesthesia? **123**
analgesia, genetic factors, The pharmacogenetics of codeine metabolism in an urban population of children and its implications for analgesic reliability **839**
analgesia, obstetric, Epidural analgesia and backache a randomized controlled comparison with intramuscular meperidine for analgesia during labour **466**
Patient-controlled epidural analgesia *versus* continuous infusion for labour analgesia: a meta-analysis **459**
analgesia, patient-controlled, Comparison of morphine alone with morphine plus clonidine for postoperative patient-controlled analgesia **424**
Effectiveness of acute postoperative pain management I. Evidence from published data **409**
Patient-controlled epidural analgesia *versus* continuous infusion for labour analgesia. a meta-analysis **459**
analgesia, postoperative, Comparison of intrathecal fentanyl and diamorphine in addition to bupivacaine for Caesarean section under spinal anaesthesia **452**
Methods of post-thoracotomy analgesia: *correspondence* **184**
analgesic techniques, Intraperitoneal administration of analgesia is this practice of any utility?. *editorial* **535**
analgesic techniques, epidural, Methods of post-thoracotomy analgesia. *correspondence* **184**
Patient-controlled epidural analgesia *versus* continuous infusion for labour analgesia: a meta-analysis **459**
analgesic techniques, intramuscular, Effectiveness of acute postoperative pain management: I. Evidence from published data **409**
analgesics anti-inflammatory, non-steroidal, diclofenac, Effect of diclofenac on cerebral blood flow velocity in patients with supratentorial tumours **762**
analgesics anti-inflammatory, steroid, Methods of post-thoracotomy analgesia: *correspondence* **184**
analgesics non-opioid, anandamide, Comparison of the effects of anandamide at recombinant and endogenous rat vanilloid receptors **882**
analgesics opioid, codeine, The pharmacogenetics of codeine metabolism in an urban population of children and its implications for analgesic reliability **839**
analgesics opioid, diamorphine, Comparison of intrathecal fentanyl and diamorphine in addition to bupivacaine for Caesarean section under spinal anaesthesia **452**
analgesics opioid, fentanyl, Comparison of intrathecal fentanyl and diamorphine in addition to bupivacaine for Caesarean section under spinal anaesthesia **452**
Effect of a single dose of esmolol on the bispectral index scale (BIS) during propofol/fentanyl anaesthesia **509**
Sevoflurane and propofol decrease intraocular pressure equally during non-ophthalmic surgery and recovery **764**
analgesics opioid, meperidine, Epidural analgesia and backache: a randomized controlled comparison with intramuscular meperidine for analgesia during labour **466**
Intrathecal metoclopramide reduces intrathecal meperidine induced nausea and vomiting in surgical patients *abstract* **208P**
analgesics opioid, morphine, Comparison of morphine alone with morphine plus clonidine for postoperative patient-controlled analgesia **424**
Electrophysiological effects of morphine in an *in vitro* model of the 'border zone' between normal and ischaemic–reperfused guinea-pig myocardium **888**
Intrathecal morphine overdose during combined spinal–epidural block for Caesarean delivery **925**
Is morphine-induced sedation synonymous with analgesia during intravenous morphine titration? **697**
analgesics opioid, remifentanil, Effect of remifentanil on postoperative pain in patients having fentanyl-propofol anaesthesia for cardiac surgery: *abstract* **678P**
Remifentanil compared with sufentanil during extra-corporeal shock wave lithotripsy with spontaneous ventilation: a double-blind, randomized study **567**
Remifentanil or propofol for sedation during carotid endartectomy under cervical plexus block **637**
analgesics opioid, sufentanil, Epinephrine and clonidine do not improve intrathecal sufentanil analgesia after total hip replacement **562**
Impaired explicit memory after recovery from propofol/sufentanil anaesthesia is related to changes in the midlatency auditory evoked response **376**
Remifentanil compared with sufentanil during extra-corporeal shock wave lithotripsy with spontaneous ventilation: a double-blind, randomized study **567**
antagonists benzodiazepine, midazolam, Auditory evoked response during propofol anaesthesia after pre-induction with midazolam **325**
antagonists, esmolol, Effect of a single dose of esmolol on the bispectral index scale (BIS) during propofol/fentanyl anaesthesia **509**
arterial pressure, hypertension, Haemodynamic effects of an angiotensin-converting enzyme inhibitor and angiotensin receptor antagonist during hypovolaemia in the anaesthetized pig **599**
arterial pressure, pulmonary hypertension, Investigation of the role of cyclooxygenase-2 in modulation of the pulmonary vascular response to chronic hypoxia. *abstract* **206P**

arteries, aortic aneurysm, Prone, head down for pulmonary haemorrhage: *correspondence* **185**

arteries, brachial, Transient hyperaemic response to assess vascular reactivity of skin; effect of locally iontophoresed sodium nitroprusside **265**

arteries, flow velocity, The effect of systemic compliance on the non-invasive assessment of zero-flow pressure in a bench model of pulsatile flow: *abstract* **196P**

arteries, vascular compliance, Factors affecting the siphon effect in simulated cerebral circulation using a bench model: *abstract* **196P**

  The effect of systemic compliance on the non-invasive assessment of zero-flow pressure in a bench model of pulsatile flow. *abstract* **196P**

arteries, vasodilators, Role of propofol and its solvent, intralipid, in nitric oxide-induced peripheral vasodilatation in dogs **492**

audit, root cause analysis, Root-cause analysis of an airway filter occlusion. a way to improve the reliability of the respiratory circuit **633**

blood, anticoagulants, heparin, High-dose tinzaparin in pregnancy and the need for urgent delivery **331**

  Hirudin and its reversal *correspondence* **524**

blood, coagulation, Effects of a new modified, balanced hydroxyethyl starch preparation (Hextend®) on measures of coagulation **722**

  Effects on coagulation of intravenous crystalloid or colloid in patients undergoing peripheral vascular surgery **226**

  In vivo effect of haemodilution with saline on coagulation *correspondence* **934**

blood, erythrocytes, The development of a flow cytometric technique for tracking transfused allogeneic red blood cells: *abstract* **197P**

  The survival of transfused red blood cells in critically ill patients. *abstract* **197P**

blood, flow, colonic, Effect of thoracic epidural anaesthesia on colonic blood flow **446**

blood, haemodilution, Effects on coagulation of intravenous crystalloid or colloid in patients undergoing peripheral vascular surgery **226**

  In vivo effect of haemodilution with saline on coagulation *correspondence* **934**

blood, haemodynamics, Role of propofol and its solvent, intralipid, in nitric oxide-induced peripheral vasodilatation in dogs **492**

blood, intravascular bubbles, Expansion of air bubbles in aqueous solutions of nitrous oxide or xenon **282**

blood, loss, Platelet function point-of-care tests in post-bypass cardiac surgery: are they relevant? **715**

blood, massive haemoptysis, Prone, head down for pulmonary haemorrhage: *correspondence* **185**

blood, plasma, Stereoselective *in vitro* degradation pattern of mivacurium in human plasma **832**

blood, platelets, Platelet function assessment in Glanzmann's thrombasthenia: *correspondence* **525**

  Platelet function point-of-care tests in post-bypass cardiac surgery: are they relevant? **715**

blood, transfusion, Blood transfusion in surgical practice—matching supply to demand *editorial* **214**

  Should we demand fresh red blood cells for perioperative and critically ill patients?: *editorial* **537**

  The survival of transfused red blood cells in critically ill patients *abstract* **197P**

  Validation of a clinical prediction rule to reduce preoperative type and screen procedures **221**

blood, volume replacement, Effects of a new modified, balanced hydroxyethyl starch preparation (Hextend®) on measures of coagulation **722**

blood, volume, cerebral, Regional response of cerebral blood volume to graded hypoxic hypoxia in rat brain **287**

book reviews, *Accident and Emergency Diagnosis and Management* **530**

  Anaesthesia for the High Risk Patient **803**

  Anaesthesia OSCE. 2nd Edition **532**

  Anesthesia and Neurosurgery **189**

  Anesthesia for the Cardiac Patient **664**

  Atlas of Common Pain Syndromes **667**

  Atlas of Hemofiltration **191**

  Basic Statistics and Epidemiology: A Practical Guide **943**

  Cardiac Arrhythmias Practical Notes on Interpretation and Treatment **532**

  Cardiogenic Shock: Diagnosis and Treatment **665**

  Clinical Anesthesia Practice **664**

  Clinical Data Interpretation in Anaesthesia and Intensive Care **942**

  Concise Anatomy for Anaesthesia **346**

  Critical Care Focus. Number 8. Blood and Blood Transfusion **531**

  Critical Care Medicine: Principles of Diagnosis and Management in the Adult **190**

  Fundamental Principles and Practice of Anaesthesia **940**

  Handbook of Obstetric Anaesthesia **531**

  Heal the Pain, Comfort the Spirit **667**

  How to Survive in Anaesthesia **804**

  International Anesthesiology Clinics Preoperative Evaluation and Cost Containment **943**

  Key Topics in Chronic Pain **193**

  Manual of Pain Management **666**

  Notable Names in Anaesthesia **805**

  Oxford Handbook of Anaesthesia **346**

  Pediatric Anesthesia: Principles and Practice **191**

  Practical Pain Management **666**

  Prescription for Learning **347**

  Problems in Anesthesia Series Cardiothoracic Surgery **347**

  Problems in Anesthesia Series Quality, Safety, Risk and Outcomes **942**

  Problems in Anesthesia Series Traumacare **530**

  Pulse Oximetry **802**

  Safe Retrieval and Transfer: the Practical Approach **190**

  Shnider and Levinson's Anesthesia for Obstetrics **192**

  Spinal Cord Injury Pain Assessment, Mechanisms, and Management **803**

  The Year in Hypertension 2001 **191**

  The Year in Interventional Cardiology: 2002 **665**

  Uncommon Problems in Intensive Care **346**

brain, Attempting to estimate the rate of perfusion of the cerebral site of action of sevoflurane (2): *abstract* **202P**

brain, arcuate nucleus, Neuroprotective and neurotoxic properties of the 'inert' gas, xenon **739**

brain, blood flow, Cerebral haemodynamics in pregnancy and pre-eclampsia as assessed by transcranial Doppler ultrasonography **687**

brain, brain stem, What can *in vivo* electrophysiology in animal models tell us about mechanisms of anaesthesia? **123**

brain, cerebral blood flow, Cerebrovascular carbon dioxide reactivity in children anaesthetized with sevoflurane: *correspondence* **525**

  Effect of diclofenac on cerebral blood flow velocity in patients with supratentorial tumours **762**

  The effects of dopexamine on cerebral carbon dioxide reactivity *abstract* **204P**

  Factors affecting the siphon effect in simulated cerebral circulation using a bench model *abstract* **196P**

brain, cerebral cortex, *In vitro* networks: cortical mechanisms of anaesthetic action **102**

brain, cerebral ischaemia, Effects of mild and moderate hypothermia on apoptosis in neuronal PC12 cells **301**

brain, dopexamine, The effects of dopexamine on cerebral carbon dioxide reactivity: *abstract* **204P**

brain, evoked potentials, Auditory evoked response during propofol anaesthesia after pre-induction with midazolam **325**

  Changes in the rapidly extracted auditory evoked potentials index and the bispectral index during sedation induced by propofol or midazolam under epidural block **260**

  Impaired explicit memory after recovery from propofol/sufentanil anaesthesia is related to changes in the midlatency auditory evoked response **376**

brain, GABA$_A$ receptor, *In vitro* networks cortical mechanisms of anaesthetic action **102**

  What can *in vivo* electrophysiology in animal models tell us about mechanisms of anaesthesia? **123**

brain, ischaemia, Apparent diffusion coefficient mapping predicts mortality and outcome in rats with intracerebral haemodynamic disturbance. potential role of intraoperative diffusion and perfusion weighted magnetic resonance imaging to detect cerebral ischaemia **605**

brain, magnetic resonance imaging, Regional response of cerebral blood volume to graded hypoxic hypoxia in rat brain **287**

brain, posterior cingulate and retrosplenial cortices, Neuroprotective and neurotoxic properties of the 'inert' gas, xenon **739**

brain, reticular formation, What can *in vivo* electrophysiology in animal models tell us about mechanisms of anaesthesia? **123**
brain, somatosensory cortex, What can *in vivo* electrophysiology in animal models tell us about mechanisms of anaesthesia? **123**
brain, somatosensory system, Differential effects of isoflurane on excitatory and inhibitory synaptic inputs to thalamic neurones *in vivo* **294**
brain, synapses, Anaesthetic modulation of synaptic transmission in the mammalian CNS **79**
  Concepts and correlations relevant to general anaesthesia **3**
  Current assessment of targets and theories of anaesthesia **167**
brain, thalamus, Differential effects of isoflurane on excitatory and inhibitory synaptic inputs to thalamic neurones *in vivo* **294**
brain, zeroflow pressure, Factors affecting the siphon effect in simulated cerebral circulation using a bench model: *abstract* **196P**
  The effect of systemic compliance on the non-invasive assessment of zero-flow pressure in a bench model of pulsatile flow· *abstract* **196P**
brian, thalamus, What can *in vivo* electrophysiology in animal models tell us about mechanisms of anaesthesia? **123**

Caenorhabditis elegans, *In vivo* genetics of anaesthetic action **143**
carbon dioxide, The effects of dopexamine on cerebral carbon dioxide reactivity: *abstract* **204P**
carbon dioxide, measurement, Comparison of oesophageal and gastric air tonometry in patients with circulatory failure **237**
carbon dioxide, partial pressure, Comparison of oesophageal and gastric air tonometry in patients with circulatory failure **237**
cardiovascular system, responses, Retroperitoneoscopic excision of phaeochromocytoma: *correspondence* **188**
care delivery, A hospital-wide in-patient survey of level of care delivery. preliminary results· *abstract* **349P**
care period, augmented, Is the ACP data set accurate? A network-based survey: *abstract* **350P**
CD review, *The Electronic Anesthesiology Library (TEAL) on CD-ROM* **940**
cells, apoptosis, Effects of mild and moderate hypothermia on apoptosis in neuronal PC12 cells **301**
children, BIS—cautionary interpretation of data in children. *abstract* **672P**
  Fluoride excretion in children after sevoflurane anaesthesia **693**
  Sevoflurane anaesthesia in children after induction of anaesthesia with midazolam and thiopental does not cause epileptiform EEG **853**
complications, Confidential enquiries into maternal deaths, 1997–1999: *editorial* **369**
  Maternal deaths from anaesthesia An extract from *Why Mothers Die 1997–1999,* the Confidential Enquiries into Maternal Deaths in the United Kingdom **499**
  Sudden upper airway obstruction due to invisible rain-out in the heat and moisture exchange filter: *correspondence* **335**
  Transtracheal high frequency jet ventilation and iatrogenic injury: *correspondence* **184**
complications, acute lung injury, How effective are lung recruitment manoeuvres in acute lung injury?. *abstract* **356P**
complications, acute renal failure, Perioperative fluid management and the incidence of acute renal failure following coronary artery bypass surgery. *abstract* **358P**
complications, acute respiratory distress syndrome, Early hypoxaemia is a marker of outcome for pulmonary but not extrapulmonary acute respiratory distress syndrome: *abstract* **351P**
complications, air embolism, Air embolism. diagnosis with single-photon emission tomography and successful hyperbaric oxygen therapy **775**
complications, amnesia, Current assessment of targets and theories of anaesthesia **167**
complications, arrhythmia, Use of implantable cardioverter defibrillator and anti-arrhythmic agents in a parturient **652**
complications, aspiration, The effect of ranitidine on gastro-oesophageal acid reflux and tracheal acid aspiration· a randomized study of patients in the thoracotomy position: *abstract* **203P**
complications, backache, Epidural analgesia and backache: a randomized controlled comparison with intramuscular meperidine for analgesia during labour **466**
complications, beta-thalassaemia major, Submental intubation *versus* tracheostomy· *correspondence* **344**
complications, bradycardia, Anaesthetic management of severe bradycardia during general anaesthesia using temporary cardiac pacing **655**
complications, Brugada syndrome, General anaesthesia in a patient with Brugada syndrome **788**
complications, burns, Is A2 flag a predictor of mortality in burns patients *abstract* **198P**
  Pharmacodynamics of mivacurium chloride in 12- to 18-yr-old adolescents with thermal injury **580**
complications, cancer, Do critically ill patients with haematological malignancy survive intensive care and beyond? *abstract* **359P**
complications, cardiac arrest, A prospective audit of the incidence of physiological monitoring in the 24h before a cardiac arrest in a district general hospital: *abstract* **353P**
  Can an early warning scoring system identify physiological deterioration in patients who later suffer a cardiac arrest? *abstract* **353P**
  Delays in defibrillation influence of different monitoring techniques **405**
  Live and let die? A structured approach to decision-making about resuscitation *editorial* **683**
complications, cardiorespiratory arrest, Prediction of neurological outcome following outside hospital cardio-respiratory arrest. *correspondence* **660**
complications, catheter colonization, Time course for internal jugular and subclavian central venous catheter tip colonization *abstract* **349P**
complications, catheter damage, The stuck central venous catheter beware of potential hazards **650**
complications, chronic respiratory disease, Factors associated with intensive care outcome in patients with severe chronic respiratory disease· *abstract* **352P**
complications, convulsions, Unexplained fitting in three parturients suffering from postdural puncture headache **782**
complications, deep vein thrombosis, High-dose tinzaparin in pregnancy and the need for urgent delivery **331**
complications, defective equipment, Cuffed Portex tracheal tube *correspondence* **187**
complications, difficult intubation, Anaesthesia in an adult with Rubenstein-Taybi syndrome using the ProSeal laryngeal mask airway **786**
complications, epidural abscess, Epidural abscess complicating insertion of epidural catheters **778**
complications, equipment problems, Equipment problems during anaesthesia—are they a quality problem? **825**
complications, Glanzmann's thrombasthenia, Platelet function assessment in Glanzmann's thrombasthenia *correspondence* **525**
complications, haemoglobinopathy, Submental intubation *versus* tracheostomy: *correspondence* **344**
complications, herbal medicines, Preoperative use of herbal medicines a patient survey **792**
complications, hypertension, Coronary artery spasm and non-Q-wave myocardial infarction following intravenous ephedrine in two healthy women under spinal anaesthesia **519**
complications, hypervolaemia, Haemodynamic effects of an angiotensin-converting enzyme inhibitor and angiotensin receptor antagonist during hypovolaemia in the anaesthetized pig **599**
  Pathophysiology and clinical implications of perioperative fluid excess **622**
complications, hypoxia, Regional response of cerebral blood volume to graded hypoxic hypoxia in rat brain **287**
complications, infections, Management of failed intubation in a septic parturient **328**
  Management of failed intubation in a septic parturient: *correspondence* **937**
complications, intubation tracheal, Management of failed intubation in a septic parturient **328**
  Management of failed intubation in a septic parturient *correspondence* **937**
complications, learning difficulties, Spontaneous breathing combined with high frequency ventilation during bronchoscopic resection of a large tracheal tumour **641**
complications, ligament rupture, Posterior spinal ligament rupture associated with laryngeal mask insertion in a patient with undisclosed unstable cervical spine **514**
complications, mediastinitis, Complete airway obstruction in a ventilated patient after oesophageal dilation **517**

complications, morbidity, Atracurium is associated with postoperative residual curarization **766**

complications, muscular atrophy, Postoperative use of a cough-assist device in avoiding prolonged intubation **644**

complications, neurological, Pencil point spinal needles and neurological damage: *correspondence* **800**

complications, nosocomial pneumonia, Alveolar and serum oxidative stress in ventilation-associated pneumonia **231**

complications, obstruction, Mechanical closure of the vocal cords with the LMA ProSeal™: *correspondence* **936**

complications, oedema, Management of a known difficult airway in a morbidly obese patient with gross supraglottic oedema secondary to thyroid disease **927**

complications, overdose, Intrathecal morphine overdose during combined spinal–epidural block for Caesarean delivery **925**

complications, oxidative stress, Alveolar and serum oxidative stress in ventilation-associated pneumonia **231**

complications, Parkinson's disease, Parkinson's disease and anaesthesia **904**

complications, phaeochromocytoma, Retroperitoneoscopic excision of phaeochromocytoma: *correspondence* **188**

complications, phenylephrine, Management of intraoperative pulmonary oedema in a child following systemic absorption of phenylephrine eyedrops *correspondence* **343**

complications, pneumonia, Decreased intragastric production of nitric oxide could predispose to ventilator-associated pneumonia: *abstract* **356P**

complications, postdural puncture headache, Unexplained fitting in three parturients suffering from postdural puncture headache **782**

complications, postoperative, Atracurium is associated with postoperative residual curarization **766**

complications, pre-eclampsia, Cerebral haemodynamics in pregnancy and pre-eclampsia as assessed by transcranial Doppler ultrasonography **687**

  Change in snoring as a predictive factor for pre-eclampsia: *abstract* **678P**

complications, quadriplegia, Flow-by induced hypoventilation in high spinal cord lesions—report of two cases **512**

  Pressure support ventilation and the critically ill patient with muscle weakness: *editorial* **373**

complications, respiratory, Bilateral pleural effusions: unexpected complication after left internal jugular venous catheterization for total parenteral nutrition **647**

  Postoperative use of a cough-assist device in avoiding prolonged intubation **644**

  Remifentanil compared with sufentanil during extra-corporeal shock wave lithotripsy with spontaneous ventilation. a double-blind, randomized study **567**

  Spontaneous breathing combined with high frequency ventilation during bronchoscopic resection of a large tracheal tumour **641**

complications, Rubenstein-Taybi syndrome, Anaesthesia in an adult with Rubenstein-Taybi syndrome using the ProSeal laryngeal mask airway **786**

complications, sepsis, Inflammation and the coagulation system: *editorial* **216**

complications, spinal cord trauma, Pain and injury from epidural injection. *correspondence* **188**

complications, thrombocytopenia, Hirudin and its reversal: *correspondence* **524**

complications, thrombosis, Probable allergic reaction to cyclosporin and early formation of thrombi on a pulmonary artery catheter: two unusual complications during bilateral lung transplantation **930**

complications, trauma, Missed injury in major trauma in the adult intensive care unit: *abstract* **351P**

  Quality of pre-hospital emergency ventilation in patients with severe head injury: *correspondence* **936**

complications, vascular reactivity, Transient hyperaemic response to assess vascular reactivity of skin; effect of locally iontophoresed sodium nitroprusside **265**

complications, warfare, Chemical and biological weapons Implications for anaesthesia and intensive care **306**

  Management of casualties from terrorist chemical and biological attack: a key role for the anaesthetist: *editorial* **211**

cough, Functional magnetic nerve stimulation of the abdominal muscles developmental of an artificial cough: *abstract* **205P**

  Postoperative use of a cough-assist device in avoiding prolonged intubation **644**

***Danio rerio*,** *In vivo* genetics of anaesthetic action **143**

***Drosophila melanogaster*,** *In vivo* genetics of anaesthetic action **143**

education, Training course in local anaesthesia of the airway and fibreoptic intubation using course delegates as subjects **586**

education, junior staff, Posture used by anaesthetists during laryngoscopy **772**

enzymes, aconitase, Comparison of aconitase activity in patients and a rat model of septic shock: *abstract* **352P**

enzymes, angiotensin-converting enzyme, Haemodynamic effects of an angiotensin-converting enzyme inhibitor and angiotensin receptor antagonist during hypovolaemia in the anaesthetized pig **599**

enzymes, cyclooxygenase-2, Investigation of the role of cyclooxygenase-2 in modulation of the pulmonary vascular response to chronic hypoxia. *abstract* **206P**

enzymes, cytochrome P450 CYP2D6, The pharmacogenetics of codeine metabolism in an urban population of children and its implications for analgesic reliability **839**

enzymes, manganese superoxide dismutase, Genetic analysis of the MnSOD gene in patients with sepsis: *abstract* **199P**

enzymes, nitric oxide synthase, 7-Nitroindazole reduces spontaneous activity in wild-type and nitric oxide synthase type I gene-deleted mice. *abstract* **202P**

  7-Nitroindazole reduces the MAC of isoflurane in wild-type and type I nitric oxide synthase knockout mice: *abstract* **201P**

enzymes, plasma cholinesterase, Pharmacodynamics of mivacurium chloride in 12- to 18-yr-old adolescents with thermal injury **580**

enzymes, protein kinase C, Anaesthetic actions on other targets: protein kinase C and guanine nucleotide-binding proteins **62**

enzymes, tumour necrosis factor α cleaving enzyme, TNFα cleaving enzyme (TACE) activity assessed by TIMP-3 binding. *abstract* **676P**

equipment, airway, Cuffed Portex tracheal tube. *correspondence* **187**

equipment, bacterial filters, Sudden upper airway obstruction due to invisible rain-out in the heat and moisture exchange filter: *correspondence* **335**

equipment, catheters, Probable allergic reaction to cyclosporin and early formation of thrombi on a pulmonary artery catheter. two unusual complications during bilateral lung transplantation **930**

  The stuck central venous catheter: beware of potential hazards **650**

  Time course for internal jugular and subclavian central venous catheter tip colonization: *abstract* **349P**

equipment, catheters central venous, Bilateral pleural effusions: unexpected complication after left internal jugular venous catheterization for total parenteral nutrition **647**

  Use of central venous catheters in intensive care: *abstract* **363P**

equipment, catheters tube exchange, Fibreoptic tracheal intubation after placement of the laryngeal tube **733**

equipment, cell savers, the influence of cell saver on transfusion requirements during elective abdominal aortic aneurysm repair: *abstract* **362P**

equipment, cuffs tracheal, Maintenance of stable cuff pressure in the Brandt™ tracheal tube during anaesthesia with nitrous oxide **271**

equipment, defibrillators, Delays in defibrillation: influence of different monitoring techniques **405**

equipment, fibreoptic sensor, Use of the Paratrend© sensor to measure the partial pressures of oxygen and carbon dioxide in the liver tissue of patients undergoing liver resection: *abstract* **201P**

equipment, flurometric imaging plate reader, Comparison of the effects of anandamide at recombinant and endogenous rat vanilloid receptors **882**

equipment, gum elastic bougie, Comparison of the peak forces that can be exerted by multiple-use and single-use bougies in vitro: *abstract* **671P**

equipment, heat and moisture exchange filters, Comparison of two techniques for measuring penetration of sodium chloride particles through breathing system filters **541**

equipment, heat and moisture exchangers, Sudden upper airway obstruction due to invisible rain-out in the heat and moisture exchange filter: *correspondence* **335**

equipment, laryngoscopes, Comparison of two Macintosh laryngoscope blades: *abstract* **670P**
equipment, laryngoscopes fibreoptic, A clinical appraisal of the Bonfils Intubating Fibrescope: *abstract* **671P**
equipment, mannequin, Posture used by anaesthetists during laryngoscopy **772**
equipment, masks anaesthesia, Anaesthesia in an adult with Rubenstein-Taybi syndrome using the ProSeal laryngeal mask airway **786**
  Mechanical closure of the vocal cords with the LMA ProSeal^{TM} *correspondence* **936**
  Posterior spinal ligament rupture associated with laryngeal mask insertion in a patient with undisclosed unstable cervical spine **514**
  The laryngeal tube compared with the laryngeal mask insertion, gas leak pressure and gastric insufflation **729**
  Use of the Intubating Laryngeal Mask in failed intubation associated with amyloid macroglossia: *correspondence* **186**
equipment, Multichannel Discrete Analyzer, Is A2 flag a predictor of mortality in burns patients?: *abstract* **198P**
equipment, needles, Bacterial contamination of epidural needles after multiple skin passes **922**
equipment, pulse oximeter, The influence of hydrogen ion concentration and haemoglobin concentration on the accuracy of the pulse oximeter (<SpO2>): *abstract* **360P**
equipment, Robertshaw double lumen tube, An audit of Robertshaw double lumen tube placement using the fibreoptic bronchoscope: *correspondence* **661**
equipment, Thrombelastograph®, Effects on coagulation of intravenous crystalloid or colloid in patients undergoing peripheral vascular surgery **226**
equipment, tubes laryngeal, Fibreoptic tracheal intubation after placement of the laryngeal tube **733**
  The laryngeal tube compared with the laryngeal mask: insertion, gas leak pressure and gastric insufflation **729**
equipment, tubes tracheal, Maintenance of stable cuff pressure in the Brandt^{TM} tracheal tube during anaesthesia with nitrous oxide **271**
  Submental intubation *versus* tracheostomy: *correspondence* **344**
equipment, tubes tracheostomy, Tracheostomy management after intensive care: a survey of current practice in the UK *abstract* **350P**
equipment, ventilators, Why change a patient's ventilatory system? A comparison of continuous positive airway pressure (SPAP) through the Galileo ventilator *vs* a Drager CF800 device: *abstract* **366P**
eye, intraocular pressure, Sevoflurane and propofol decrease intraocular pressure equally during non-ophthalmic surgery and recovery **764**
eye, ocular microtremor, Comparison of ocular microtremor and bispectral index during sevoflurane anaesthesia **551**

fluid balance, Pathophysiology and clinical implications of perioperative fluid excess **622**
fluids, i.v., Bilateral pleural effusions: unexpected complication after left internal jugular venous catheterization for total parenteral nutrition **647**
fluids, replacement, Comparison of flow guided versus conventional volume replacement in major elective surgery: *abstract* **674P**
  Fluid replacement during Picolax® bowel preparation: the consequences for anaesthesia: *abstract* **674P**

gastrointestinal tract, gastroesophageal reflux, Anaesthesia in an adult with Rubenstein-Taybi syndrome using the ProSeal laryngeal mask airway **786**
  The effect of ranitidine on gastro-oesophageal acid reflux and tracheal acid aspiration: a randomized study of patients in the thoracotomy position: *abstract* **203P**
gastrointestinal tract, intestinal mucosa, Lactic acidosis in the rectal lumen of patients with septic shock measured by luminal equilibrium dialysis **919**
gastrointestinal tract, oesophagus, Complete airway obstruction in a ventilated patient after oesophageal dilation **517**
genetic factors, *In vivo* genetics of anaesthetic action **143**

heart, arrhythmia, Electrophysiological effects of morphine in an *in vitro* model of the 'border zone' between normal and ischaemic–reperfused guinea-pig myocardium **888**
  Use of implantable cardioverter defibrillator and anti-arrhythmic agents in a parturient **652**
heart, arrhythmia, bradycardia, Anaesthetic management of severe bradycardia during general anaesthesia using temporary cardiac pacing **655**
heart, arrhythmia, tachycardia, Coronary artery spasm and non-Q-wave myocardial infarction following intravenous ephedrine in two healthy women under spinal anaesthesia **519**
  The output of two sevoflorane vaporizers in the presence of helium *correspondence* **797**
heart, cardiac output, Haemodynamic effects of the prone position for spinal surgery: TIVA versus inhalation anaesthesia: *abstract* **674P**
  Is comparison of changes in cardiac output, assessed by different methods, better than only comparing cardiac output to the reference method?. *correspondence* **336**
heart, cardiopulmonary bypass, Exhaled nitric oxide as a marker of lung injury in coronary artery bypass surgery **247**
  Incidence and risk calculation of inotropic support in patients undergoing cardiac surgery with cardiopulmonary bypass using an automated anaesthesia record-keeping system **398**
heart, coronary artery bypass, Propofol attenuates myocardial lipid peroxidation during coronary artery bypass grafting surgery **242**
heart, coronary artery disease, Preoperative evaluation of patients with, or at risk of, coronary artery disease undergoing non-cardiac surgery **747**
heart, defibrillation, Successful defibrillation in the prone position *correspondence* **799**
heart, heart rate, Influence of oxygen therapy on heart rate after abdominal surgery: *abstract* **673P**
heart, inotropism, Incidence and risk calculation of inotropic support in patients undergoing cardiac surgery with cardiopulmonary bypass using an automated anaesthesia record-keeping system **398**
heart, ischaemia, Electrophysiological effects of morphine in an *in vitro* model of the 'border zone' between normal and ischaemic–reperfused guinea-pig myocardium **888**
heart, myocardial function, Pharmacological preconditioning: comparison of desflurane, sevoflurane, isoflurane and halothane in rabbit myocardium **486**
heart, pacemakers artificial, Use of implantable cardioverter defibrillator and anti-arrhythmic agents in a parturient **652**
heart, reperfusion arrhythmia, Sevoflurane preconditions stunned myocardium in septic but not healthy isolated rat hearts **896**
heart, reperfusion injury, Electrophysiological effects of morphine in an *in vitro* model of the 'border zone' between normal and ischaemic–reperfused guinea-pig myocardium **888**
heart, stroke volume, Stroke volume variation: a cardiac preload parameter in mechanically ventilated patients with severe sepsis?: *abstract* **194P**
heart, ventricular fibrillation, Successful defibrillation in the prone position: *correspondence* **799**
hormones, renin, Haemodynamic effects of an angiotensin-converting enzyme inhibitor and angiotensin receptor antagonist during hypovolaemia in the anaesthetized pig **599**
hypnotics benzodiazepine, midazolam, Changes in the rapidly extracted auditory evoked potentials index and the bispectral index during sedation induced by propofol or midazolam under epidural block **260**
  Contribution of midazolam and its 1-hydroxy metabolite to preoperative sedation in children: a pharmacokinetic-pharmacodynamic analysis **428**
  Sevoflurane anaesthesia in children after induction of anaesthesia with midazolam and thiopental does not cause epileptiform EEG **853**
  Mechanisms of action of midazolam on expression of contextual fear in rats **614**
hypothermia, Effects of mild and moderate hypothermia on apoptosis in neuronal PC12 cells **301**
hypoxaemia, Non-invasive estimation of shunt. comparison of different hypoxaemia indices: *abstract* **206P**

immune response, Probable allergic reaction to cyclosporin and early formation of thrombi on a pulmonary artery catheter: two unusual complications during bilateral lung transplantation **930**
  Xenon has no effect on cytokine balance and adhesion molecule expression within an isolated cardiopulmonary bypass system **546**
induction, anaesthesia, Influence of fresh gas and circuit on induction of anaesthesia with sevoflurane: *abstract* **673P**

infection, bacterial, Bacterial contamination of epidural needles after multiple skin passes 922
  Large variation in MRSA policies, procedures, and prevalence in English intensive care units. A questionnaire analysis: *abstract* 354P
infection, biological warfare, Chemical and biological weapons. Implications for anaesthesia and intensive care 306
  Management of casualties from terrorist chemical and biological attack. a key role for the anaesthetist: *editorial* 211
infection, pulmonary, Postoperative use of a cough-assist device in avoiding prolonged intubation 644
infection, sepsis, Genetic analysis of the MnSOD gene in patients with sepsis: *abstract* 199P
  Genetic analysis of TREM-1 a novel inflammatory receptor *abstract* 199P
  Lactic acidosis in the rectal lumen of patients with septic shock measured by luminal equilibrium dialysis 919
  Sevoflurane preconditions stunned myocardium in septic but not healthy isolated rat hearts 896
  Stroke volume variation a cardiac preload parameter in mechanically ventilated patients with severe sepsis?: *abstract* 194P
infection, septic shock, Comparison of aconitase activity in patients and a rat model of septic shock: *abstract* 352P
  Proinflammatory modifications of lipoprotein structure and function in patients with septic shock: relationship to outcome: *abstract* 361P
intensive care, Chemical and biological weapons Implications for anaesthesia and intensive care 306
  Inflammation and the coagulation system *editorial* 216
  Ventilating in recovery—the way forward. intensive therapy or critical care?: *correspondence* 526
intensive care, audit, Advanced directive questionnaire survey of intensive care staff: *abstract* 355P
  An assessment of the temperature component of the early warning score: *abstract* 367P
  Dilemmas with early warning scores: *abstract* 365P
  Do critically ill patients with haematological malignancy survive intensive care and beyond? *abstract* 359P
  Early warning scores and duration of hospital stay *abstract* 365P
  Large variation in MRSA policies, procedures, and prevalence in English intensive care units A questionnaire analysis: *abstract* 354P
  Let's reach out for outreach in critical care: *abstract* 364P
  Observations in 50 consecutive medical admissions to an adult intensive care unit in a district general hospital. an admission diagnosis of respiratory failure does not affect the likelihood of monitoring ventilatory frequency and oxygen saturation: *abstract* 364P
  Secondary inter-hospital transfers of critically ill patients: completing the audit cycle. *abstract* 354P
  The longer the patient is in hospital before ICU admission the higher the mortality. *abstract* 356P
  Use of critical care following elective repair of abdominal aortic aneurysm in four different institutions: *abstract* 355P
  When is a patient too sick for ICU admission? A case report and database analysis: *abstract* 357P
intensive care, depression, Stress in UK intensive care unit doctors 873
intensive care, nutrition, The effects of immunonutrition on clinical outcome in the critically ill: *abstract* 363P
intensive care, occupational stress, Stress in UK intensive care unit doctors 873
intensive care, organ donation, The pattern of organ donation after CVA from ICUs in the UK in the last 7 yr: *abstract* 359P
  The pattern of organ donation after trauma from ICUs in the UK in the last 7 yr: *abstract* 360P
intensive care, warfare, Management of casualties from terrorist chemical and biological attack: a key role for the anaesthetist. *editorial* 211
interactions (drug), Preoperative use of herbal medicines: a patient survey 792
intubation tracheal, Comparison of the peak forces that can be exerted by multiple-use and single-use bougies in vitro. *abstract* 671P
  Risk of accidental extubation with disposable tonsillectomy instruments. *correspondence* 659
  Spontaneous breathing combined with high frequency ventilation during bronchoscopic resection of a large tracheal tumour 641
  Prediction of the haemodynamic response to tracheal intubation comparison of laser-Doppler skin vasomotor reflex and pulse wave reflex 389
  Quality of pre-hospital emergency ventilation in patients with severe head injury *correspondence* 936
  Submental intubation *versus* tracheostomy: *correspondence* 344
  Use of the Intubating Laryngeal Mask in failed intubation associated with amyloid macroglossia: *correspondence* 186
intubation tracheal, difficult, Comparison of two Macintosh laryngoscope blades *abstract* 670P
intubation tracheal, haemodynamic changes, Esmolol prevents movement and attenuates the BIS response to orotracheal intubation 857
intubation tracheal, technique, Fibreoptic tracheal intubation after placement of the laryngeal tube 733
  Optimal rocuronium dose for intubation during inhalation induction with sevoflurane in children 277
intubation tracheal, training, Training course in local anaesthesia of the airway and fibreoptic intubation using course delegates as subjects 586
intubation, fibreoptic, Management of a known difficult airway in a morbidly obese patient with gross supraglottic oedema secondary to thyroid disease 927
ions, calcium, Phenotyping malignant hyperthermia susceptibility by measuring halothane-induced changes in myoplasmic calcium concentration in cultured human skeletal muscle cells 571
ions, ion channels, *In vivo* genetics of anaesthetic action 143
  Molecular modelling of specific and non-specific anaesthetic interactions 32
ions, ion channels, ligand-gated, The effects of general anaesthetics on ligand-gated ion channels 41
ions, ion channels, voltage-gated, Mechanisms of (local) anaesthetics on voltage-gated sodium and other ion channels 52
ions, magnesium, Evaluation of effects of magnesium sulphate in reducing intraoperative anaesthetic requirements 594

kidney, function, Urinary TGF-β is elevated following cardiac surgery and is reduced following methylprednisolone administration *abstract* 195P
kidney, urine, Fluoride excretion in children after sevoflurane anaesthesia 693

larynx, cricoid pressure, intragastric pressure, Intragastric pressure in 100 paralysed surgical patients: *abstract* 203P
larynx, laryngoscopy, Transtracheal high frequency jet ventilation and iatrogenic injury. *correspondence* 184
ligament, posterior spinal, Posterior spinal ligament rupture associated with laryngeal mask insertion in a patient with undisclosed unstable cervical spine 514
liver, tissue oxygenation, Use of the Paratrend© sensor to measure the partial pressures of oxygen and carbon dioxide in the liver tissue of patients undergoing liver resection *abstract* 201P
liver, transplantation, Is comparison of changes in cardiac output, assessed by different methods, better than only comparing cardiac output to the reference method?: *correspondence* 336
lung, acute respiratory distress syndrome, Recruitment manoeuvre on high frequency oscillation ventilation: *correspondence* 796
lung, angiectasia, Prone, head down for pulmonary haemorrhage. *correspondence* 185
lung, damage, Bilateral pleural effusions: unexpected complication after left internal jugular venous catheterization for total parenteral nutrition 647
  Exhaled nitric oxide as a marker of lung injury in coronary artery bypass surgery 247
lung, interpleural space, Bilateral pleural effusions: unexpected complication after left internal jugular venous catheterization for total parenteral nutrition 647
lung, mini-bronchoalveolar lavage, Alveolar and serum oxidative stress in ventilation-associated pneumonia 231
lung, mucus, Postoperative use of a cough-assist device in avoiding prolonged intubation 644
lung, tidal volume, Flow-by induced hypoventilation in high spinal cord lesions—report of two cases 512
  Pressure support ventilation and the critically ill patient with muscle weakness: *editorial* 373

measurement techniques, B-mode ultrasound, Effects of prolonged head-down tilt on internal jugular vein cross-sectional area **769**

measurement techniques, cytometry, The development of a flow cytometric technique for tracking transfused allogeneic red blood cells: *abstract* **197P**

measurement techniques, diffusion-weighted magnetic resonance image, Apparent diffusion coefficient mapping predicts mortality and outcome in rats with intracerebral haemodynamic disturbance: potential role of intraoperative diffusion and perfusion weighted magnetic resonance imaging to detect cerebral ischaemia **605**

measurement techniques, Doppler ultrasound, Cerebral haemodynamics in pregnancy and pre-eclampsia as assessed by transcranial Doppler ultrasonography **687**

measurement techniques, fibreoptic, An audit of Robertshaw double lumen tube placement using the fibreoptic bronchoscope: *correspondence* **661**

measurement techniques, filtration, Comparison of two techniques for measuring penetration of sodium chloride particles through breathing system filters **541**

measurement techniques, functional magnetic resonance imaging, *In vitro* imaging of anaesthetic action in humans approaches with positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) **112**

measurement techniques, laser-Doppler flowmetry, Prediction of the haemodynamic response to tracheal intubation· comparison of laser-Doppler skin vasomotor reflex and pulse wave reflex **389**

measurement techniques, MRI imaging, The effect of airway manoeuvres and route of respiration on spatial orientation of the upper airway: *abstract* **205P**

measurement techniques, non-invasive, Non-invasive estimation of shunt. comparison of different hypoxaemia indices: *abstract* **206P**

measurement techniques, open-field study, 7-Nitroindazole reduces spontaneous activity in wild-type and nitric oxide synthase type I gene-deleted mice. *abstract* **202P**

measurement techniques, outcome, Patient satisfaction with anaesthesia care development of a psychometric questionnaire and benchmarking among six hospitals in Switzerland and Austria **863**

measurement techniques, perfusion-weighted magnetic resonance image, Apparent diffusion coefficient mapping predicts mortality and outcome in rats with intracerebral haemodynamic disturbance· potential role of intraoperative diffusion and perfusion weighted magnetic resonance imaging to detect cerebral ischaemia **605**

measurement techniques, positron emission tomography, *In vitro* imaging of anaesthetic action in humans· approaches with positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) **112**

measurement techniques, pulse contour analysis, Is comparison of changes in cardiac output, assessed by different methods, better than only comparing cardiac output to the reference method? *correspondence* **336**

measurement techniques, pulse wave amplitude, Prediction of the haemodynamic response to tracheal intubation: comparison of laser-Doppler skin vasomotor reflex and pulse wave reflex **389**

measurement techniques, retroperitoneoscopy, Retroperitoneoscopic excision of phaeochromocytoma *correspondence* **188**

measurement techniques, thermodilution, Is comparison of changes in cardiac output, assessed by different methods, better than only comparing cardiac output to the reference method?: *correspondence* **336**

measurement techniques, transcranial Doppler, Effect of diclofenac on cerebral blood flow velocity in patients with supratentorial tumours **762**

measurement techniques, transient hyperaemic response, Transient hyperaemic response to assess vascular reactivity of skin, effect of locally iontophoresed sodium nitroprusside **265**

measurement techniques, transoesophageal echocardiography, Probable allergic reaction to cyclosporin and early formation of thrombi on a pulmonary artery catheter: two unusual complications during bilateral lung transplantation **930**

measurement techniques, transoesphageal Doppler, Transoesophageal Doppler measurements are tolerable and reproducible in awake, ambulatory volunteers. *abstract* **358P**

measurement techniques, ultrasound, Ultrasound-guided infraclavicular brachial plexus block **254**

membrane, ABC transporters, *In vivo* genetics of anaesthetic action **143**

membrane, stomatin, *In vivo* genetics of anaesthetic action **143**

membrane, syntaxin, *In vivo* genetics of anaesthetic action **143**

memory, Impaired explicit memory after recovery from propofol/sufentanil anaesthesia is related to changes in the midlatency auditory evoked response **376**
  Mechanisms of action of midazolam on expression of contextual fear in rats **614**

metabolism, lipid, Propofol attenuates myocardial lipid peroxidation during coronary artery bypass grafting surgery **242**

metabolism, mivacurium, Stereoselective *in vitro* degradation pattern of mivacurium in human plasma **832**

metabolism, second messengers, Saliva cyclic GMP increases during anaesthesia **635**

metabolism, sevoflurane, Fluoride excretion in children after sevoflurane anaesthesia **693**

metabolism, stereoselective, Stereoselective *in vitro* degradation pattern of mivacurium in human plasma **832**

model, computer simulation, A preliminary CoMFA model for chemically diverse intravenous general anaesthetics *abstract* **672P**
  Determining natural variation through eigenvector projections in the human airway· *abstract* **204P**

monitoring, bispectral index, Changes in the rapidly extracted auditory evoked potentials index and the bispectral index during sedation induced by propofol or midazolam under epidural block **260**
  Comparison of ocular microtremor and bispectral index during sevoflurane anaesthesia **551**
  Effect of a single dose of esmolol on the bispectral index scale (BIS) during propofol/fentanyl anaesthesia **509**
  Effects of intramuscular administration of lidocaine or bupivacaine on induction and maintenance doses of propofol evaluated by bispectral index **849**
  Esmolol prevents movement and attenuates the BIS response to orotracheal intubation **857**
  Is morphine-induced sedation synonymous with analgesia during intravenous morphine titration? **697**

monitoring, bronchial arteriography, Prone, head down for pulmonary haemorrhage: *correspondence* **185**

monitoring, depth of anaesthesia, Effect of propofol anaesthesia on the event-related potential mismatch negativity and the auditory-evoked potential N1 **382**
  Saliva cyclic GMP increases during anaesthesia **635**

monitoring, electrocardiography, Delays in defibrillation. influence of different monitoring techniques **405**

monitoring, electroencephalography, *In vitro* networks· cortical mechanisms of anaesthetic action **102**
  Sevoflurane anaesthesia in children after induction of anaesthesia with midazolam and thiopental does not cause epileptiform EEG **853**

monitoring, evoked potentials, Auditory evoked response during propofol anaesthesia after pre-induction with midazolam **325**

monitoring, intracranial pressure, A survey of the use of intracranial pressure monitoring in non-neurosurgical centres· *abstract* **366P**

monitoring, physiological, The stuck central venous catheter beware of potential hazards **650**

monitoring, point-of-care test, Platelet function point-of-care tests in post-bypass cardiac surgery· are they relevant? **715**

monitoring, ventilation, Respiratory monitoring of non-intubated patients using the 'PIPPA' breathing monitor *abstract* **677P**

Mus musculus, *In vivo* genetics of anaesthetic action **143**

muscle respiratory, Inadequate tidal volumes during biphasic pressure ventilation, caused by expiratory muscle contraction. *abstract* **209P**

muscle skeletal, contractility, Effects of halothane and isoflurane on the contraction, relaxation and energetics of rat diaphragmatic muscle **479**

muscle skeletal, diaphragm, Effects of halothane and isoflurane on the contraction, relaxation and energetics of rat diaphragmatic muscle **479**

muscle skeletal, myoblasts, Phenotyping malignant hyperthermia susceptibility by measuring halothane-induced changes in myoplasmic calcium concentration in cultured human skeletal muscle cells **571**

nerve, transmission, Anaesthetic modulation of synaptic transmission in the mammalian CNS **79**

nerves, motor neurones, *In vitro* networks: subcortical mechanisms of anaesthetic action **91**

neuromuscular block, atracurium, Atracurium is associated with postoperative residual curarization **766**

neuromuscular block, mivacurium, Pharmacodynamics of mivacurium chloride in 12- to 18-yr-old adolescents with thermal injury **580**

Stereoselective *in vitro* degradation pattern of mivacurium in human plasma **832**

neuromuscular block, rocuronium, Optimal rocuronium dose for intubation during inhalation induction with sevoflurane in children **277**

operating rooms, Mobile operating theatre. Why must it be mobile?: *correspondence* **187**

oxygen, inspired concentration, Randomized, double-blind comparison of different inspired oxygen fractions during general anaesthesia for Caesarean section **556**

oxygen, saturation, Influence of oxygen therapy on heart rate after abdominal surgery: *abstract* **673P**

pain, chronic, Actigraphic measurements of sleep variables and circadian rhythm in chronic pain patients compared with healthy controls: *abstract* **678P**

pain, experimental, Prediction of the haemodynamic response to tracheal intubation: comparison of laser-Doppler skin vasomotor reflex and pulse wave reflex **389**

pain, neuropathic, Efficacy of intravenous magnesium in neuropathic pain **711**

pain, postherpetic neuralgia, Efficacy of intravenous magnesium in neuropathic pain **711**

pain, postoperative, Effectiveness of acute postoperative pain management I. Evidence from published data **409**

Recording postoperative pain in ambulatory surgery. further evaluation of a revised electronic data collection device: *abstract* **680P**

partial pressure, oxygen, Randomized, double-blind comparison of different inspired oxygen fractions during general anaesthesia for Caesarean section **556**

pharmacodynamics, Contribution of midazolam and its 1-hydroxy metabolite to preoperative sedation in children: a pharmacokinetic-pharmacodynamic analysis **428**

pharmacokinetics, midazolam, Contribution of midazolam and its 1-hydroxy metabolite to preoperative sedation in children a pharmacokinetic-pharmacodynamic analysis **428**

pharmacokinetics, ropivacaine, Plasma concentration of ropivacaine after intercostal blocks for video-assisted thoracic surgery **251**

pharmacology, clonidine, Comparison of morphine alone with morphine plus clonidine for postoperative patient-controlled analgesia **424**

pharmacology, morphine, Comparison of morphine alone with morphine plus clonidine for postoperative patient-controlled analgesia **424**

pharmacology, nitric oxide, Exhaled nitric oxide as a marker of lung injury in coronary artery bypass surgery **247**

pharmacology, sumatriptan, Unexplained fitting in three parturients suffering from postdural puncture headache **782**

pharmacology, Synacthen, Unexplained fitting in three parturients suffering from postdural puncture headache **782**

pig, Haemodynamic effects of an angiotensin-converting enzyme inhibitor and angiotensin receptor antagonist during hypovolaemia in the anaesthetized pig **599**

polypeptides, cytokines, Genotype and IL-10 response during cardiopulmonary bypass. *abstract* **198P**

Xenon has no effect on cytokine balance and adhesion molecule expression within an isolated cardiopulmonary bypass system **546**

position, head-down tilt manoeuvre, Effects of prolonged head-down tilt on internal jugular vein cross-sectional area **769**

position, prone, Haemodynamic effects of the prone position for spinal surgery. TIVA versus inhalation anaesthesia: *abstract* **674P**

Successful defibrillation in the prone position: *correspondence* **799**

postanaesthesia care, Postoperative critical care. overnight intensive recovery. *correspondence* **344**

potency, anaesthetic, Esmolol prevents movement and attenuates the BIS response to orotracheal intubation **857**

potency, anaesthetic, MAC, 7-Nitroindazole reduces the MAC of isoflurane in wild-type and type I nitric oxide synthase knockout mice *abstract* **201P**

potency, anaesthetic, tolerance, Effect of repeated exposure on the incidence of adverse airway events during brief nasal inhalations of anaesthetics: *abstract* **670P**

prediction, preoperative, Blood transfusion in surgical practice—matching supply to demand: *editorial* **214**

Validation of a clinical prediction rule to reduce preoperative type and screen procedures **221**

pregnancy, Use of implantable cardioverter defibrillator and anti-arrhythmic agents in a parturient **652**

premedication, ranitidine, The effect of ranitidine on gastro-oesophageal acid reflux and tracheal acid aspiration: a randomized study of patients in the thoracotomy position: *abstract* **203P**

protein, c-Fos, Neuroprotective and neurotoxic properties of the 'inert' gas, xenon **739**

protein, G-proteins, Anaesthetic actions on other targets: protein kinase C and guanine nucleotide-binding proteins **62**

protein, S100β, Non-cerebral release of S100β during coronary artery bypass grafting: *abstract* **194P**

psychological responses, Mechanisms of action of midazolam on expression of contextual fear in rats **614**

publications, Interdisciplinary collaboration in anaesthesia research: *correspondence* **658**

radiotherapy, pelvic brachytherapy, Analgesia for pelvic brachytherapy: *correspondence* **342**

rat, Apparent diffusion coefficient mapping predicts mortality and outcome in rats with intracerebral haemodynamic disturbance: potential role of intraoperative diffusion and perfusion weighted magnetic resonance imaging to detect cerebral ischaemia **605**

Mechanisms of action of midazolam on expression of contextual fear in rats **614**

receptors, baroreflex, Investigation of systemic bupivacaine toxicity using the *in situ* perfused working heart-brainstem preparation of the rat: *abstract* **207P**

receptors, cannabinoid, Comparison of the effects of anandamide at recombinant and endogenous rat vanilloid receptors **882**

receptors, Trem-1, Genetic analysis of TREM-1: a novel inflammatory receptor *abstract* **199P**

receptors, vanilloid, Comparison of the effects of anandamide at recombinant and endogenous rat vanilloid receptors **882**

records, anaesthesia, computerized, Incidence and risk calculation of inotropic support in patients undergoing cardiac surgery with cardiopulmonary bypass using an automated anaesthesia record-keeping system **398**

recovery, postoperative, Patient preferences for immediate postoperative recovery **760**

Remifentanil compared with sufentanil during extra-corporeal shock wave lithotripsy with spontaneous ventilation: a double-blind, randomized study **567**

research, anaesthesia, Patient satisfaction with anaesthesia care: development of a psychometric questionnaire and benchmarking among six hospitals in Switzerland and Austria **863**

resuscitation, medical training, Effectiveness of basic airway management by junior doctors: *abstract* **208P**

risk, Incidence and risk calculation of inotropic support in patients undergoing cardiac surgery with cardiopulmonary bypass using an automated anaesthesia record-keeping system **398**

Root-cause analysis of an airway filter occlusion: a way to improve the reliability of the respiratory circuit **633**

safety, Risk of accidental extubation with disposable tonsillectomy instruments: *correspondence* **659**

safety, techniques, Pathophysiology and clinical implications of perioperative fluid excess **622**

Patient-controlled epidural analgesia *versus* continuous infusion for labour analgesia: a meta-analysis **459**

scoliosis, Postoperative use of a cough-assist device in avoiding prolonged intubation **644**

sedation, Is morphine-induced sedation synonymous with analgesia during intravenous morphine titration? **697**

Remifentanil or propofol for sedation during carotid endartectomy under cervical plexus block **637**

sedation, preoperative, Contribution of midazolam and its 1-hydroxy metabolite to preoperative sedation in children· a pharmacokinetic-pharmacodynamic analysis **428**

sensory block, anaesthetic techniques, regional, The effectiveness of the Neuropen in predicting the dermatomal limits of sensory blockade in regional anaesthesia for Caesarean section as compared with ethyl chloride. *abstract* **680P**

sleep, Actigraphic measurements of sleep variables and circadian rhythm in chronic pain patients compared with healthy controls: *abstract* **678P**
  Change in snoring as a predictive factor for pre-eclampsia: *abstract* **678P**
  In vitro networks: cortical mechanisms of anaesthetic action **102**

spinal cord, dorsal root ganglion, Comparison of the effects of anandamide at recombinant and endogenous rat vanilloid receptors **882**

spinal cord, motor block, Evaluation of S1 motor block to determine a safe, reliable test dose for epidural analgesia **442**

spinal cord, sensory block, Coronary artery spasm and non-Q-wave myocardial infarction following intravenous ephedrine in two healthy women under spinal anaesthesia **519**
  What can *in vivo* electrophysiology in animal models tell us about mechanisms of anaesthesia? **123**

statistics, Confidence in statistical analysis *editorial* **807**

statistics, risk score, Predictive models for postoperative nausea and vomiting. *correspondence* **339**

surgery, Comparison of flow guided versus conventional volume replacement in major elective surgery. *abstract* **674P**
  Patient satisfaction with anaesthesia care. development of a psychometric questionnaire and benchmarking among six hospitals in Switzerland and Austria **863**

surgery, abdominal, Effects of a new modified, balanced hydroxyethyl starch preparation (Hextend®) on measures of coagulation **722**

surgery, adenotonsillectomy, The pharmacogenetics of codeine metabolism in an urban population of children and its implications for analgesic reliability **839**

surgery, aneurysm, the influence of cell saver on transfusion requirements during elective abdominal aortic aneurysm repair. *abstract* **362P**

surgery, bronchoscopy, Prone, head down for pulmonary haemorrhage: *correspondence* **185**

surgery, cardiopulmonary bypass, Xenon has no effect on cytokine balance and adhesion molecule expression within an isolated cardiopulmonary bypass system **546**

surgery, cardiovascular, Effect of remifentanil on postoperative pain in patients having fentanyl-propofol anaesthesia for cardiac surgery: *abstract* **678P**
  Genotype and IL-10 response during cardiopulmonary bypass. *abstract* **198P**
  Incidence and risk calculation of inotropic support in patients undergoing cardiac surgery with cardiopulmonary bypass using an automated anaesthesia record-keeping system **398**
  Non-cerebral release of S100β during coronary artery bypass grafting: *abstract* **194P**
  Perioperative fluid management and the incidence of acute renal failure following coronary artery bypass surgery. *abstract* **358P**
  Platelet function point-of-care tests in post-bypass cardiac surgery· are they relevant? **715**
  Urinary TGF-β is elevated following cardiac surgery and is reduced following methylprednisolone administration. *abstract* **195P**

surgery, carotid endartectomy, Remifentanil or propofol for sedation during carotid endartectomy under cervical plexus block **637**

surgery, day-case, Recording postoperative pain in ambulatory surgery further evaluation of a revised electronic data collection device· *abstract* **680P**

surgery, gynaecological, Electronic diary records show similar symptom severity after major and intermediate gynaecological surgery· *abstract* **200P**

surgery, laparoscopy, Electronic diary records show similar symptom severity after major and intermediate gynaecological surgery *abstract* **200P**

surgery, laparotomy, Bilateral pleural effusions. unexpected complication after left internal jugular venous catheterization for total parenteral nutrition **647**

surgery, laryngoscopy, Anaesthetic management of severe bradycardia during general anaesthesia using temporary cardiac pacing **655**

surgery, laser, Transtracheal high frequency jet ventilation and iatrogenic injury: *correspondence* **184**

surgery, non-cardiac, Preoperative evaluation of patients with, or at risk of, coronary artery disease undergoing non-cardiac surgery **747**

surgery, obstetric, Comparison of intrathecal fentanyl and diamorphine in addition to bupivacaine for Caesarean section under spinal anaesthesia **452**

surgery, pectoral, Ultrasound-guided infraclavicular brachial plexus block **254**

surgery, preoperative assessment, Preoperative evaluation of patients with, or at risk of, coronary artery disease undergoing non-cardiac surgery **747**

surgery, spinal, Successful defibrillation in the prone position. *correspondence* **799**

surgery, thoracic, Methods of post-thoracotomy analgesia. *correspondence* **184**

surgery, thoractomy, The effect of ranitidine on gastro-oesophageal acid reflux and tracheal acid aspiration: a randomized study of patients in the thoracotomy position· *abstract* **203P**

surgery, total hip replacement, Spinal anaesthesia. comparison of plain ropivacaine 5 mg ml^{-1} with bupivacaine 5 mg ml^{-1} for major orthopaedic surgery **702**

sympathetic nervous system, clonidine, Epinephrine and clonidine do not improve intrathecal sufentanil analgesia after total hip replacement **562**

sympathetic nervous system, epinephrine, Epinephrine and clonidine do not improve intrathecal sufentanil analgesia after total hip replacement **562**

theories of anaesthetic action, Current assessment of targets and theories of anaesthesia **167**
  In vitro imaging of anaesthetic action in humans. approaches with positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) **112**
  In vivo characterization of clinical anaesthesia and its components **156**
  Molecular modelling of specific and non-specific anaesthetic interactions **32**

theories of anaesthetic action, molecular, Mechanisms of (local) anaesthetics on voltage-gated sodium and other ion channels **52**
  Molecular and basic mechanisms of anaesthesia· *editorial* **1**
  The effects of general anaesthetics on ligand-gated ion channels **41**

therapy, hyperbaric oxygen, Air embolism diagnosis with single-photon emission tomography and successful hyperbaric oxygen therapy **775**

toxicity, Plasma concentration of ropivacaine after intercostal blocks for video-assisted thoracic surgery **251**

toxicity, chemical warfare, Chemical and biological weapons Implications for anaesthesia and intensive care **306**
  Management of casualties from terrorist chemical and biological attack a key role for the anaesthetist *editorial* **211**

transfusion, red cell salvage, the influence of cell saver on transfusion requirements during elective abdominal aortic aneurysm repair *abstract* **362P**

transfusion, stored blood, Should we demand fresh red blood cells for perioperative and critically ill patients? *editorial* **537**

uterus, thermal ablation, Plasma lidocaine concentrations following insertion of 2% lidocaine gel into the uterine cavity after uterine balloon thermal ablation **846**

veins, complications, Coronary artery spasm and non-Q-wave myocardial infarction following intravenous ephedrine in two healthy women under spinal anaesthesia **519**

veins, jugular, cannulation, Effects of prolonged head-down tilt on internal jugular vein cross-sectional area **769**

ventilation, Quality of pre-hospital emergency ventilation in patients with severe head injury: *correspondence* **936**

ventilation, biphasic pressure ventilation, Inadequate tidal volumes during biphasic pressure ventilation, caused by expiratory muscle contraction: *abstract* **209P**

ventilation, continuous positive airway pressure, Why change a patient's ventilatory system? A comparison of continuous positive airway pressure (SPAP) through the Galileo ventilator *vs* a Drager CF800 device. *abstract* **366P**

ventilation, high frequency, Recruitment manoeuvre on high frequency oscillation ventilation: *correspondence* **796**

Transtracheal high frequency jet ventilation and iatrogenic injury: *correspondence* **184**

ventilation, high frequency jet, Spontaneous breathing combined with high frequency ventilation during bronchoscopic resection of a large tracheal tumour **641**

Transtracheal high frequency jet ventilation and iatrogenic injury. *correspondence* **184**

ventilation, hypoventilation, Flow-by induced hypoventilation in high spinal cord lesions—report of two cases **512**

Pressure support ventilation and the critically ill patient with muscle weakness· *editorial* **373**

ventilation, mechanical, Comparison of oesophageal and gastric air tonometry in patients with circulatory failure **237**

Flow-by induced hypoventilation in high spinal cord lesions—report of two cases **512**

Outcomes, cost, and long-term survival of patients referred to regional centre for weaning from mechanical ventilation *abstract* **361P**

Pressure support ventilation and the critically ill patient with muscle weakness *editorial* **373**

Survival and success of weaning from prolonged ventilation: *correspondence* **938**

The influence of diagnosis on survival and success in weaning patients from prolonged mechanical ventilation: *abstract* **362P**

ventilation, peak expiratory flow rate, Functional magnetic nerve stimulation of the abdominal muscles. developmental of an artificial cough: *abstract* **205P**

ventilation, postoperative, Postoperative use of a cough-assist device in avoiding prolonged intubation **644**

ventilation, respiratory circuit, Root-cause analysis of an airway filter occlusion: a way to improve the reliability of the respiratory circuit **633**

ventilation, spontaneous, Remifentanil compared with sufentanil during extra-corporeal shock wave lithotripsy with spontaneous ventilation: a double-blind, randomized study **567**

vomiting, antiemetic, Intrathecal metoclopramide reduces intrathecal meperidine induced nausea and vomiting in surgical patients: *abstract* **208P**

vomiting, antiemetics, ondansetron, Management of post-strabismus nausea and vomiting in children using ondansetron: a value-based comparison of outcomes **473**

vomiting, nausea, Intrathecal metoclopramide reduces intrathecal meperidine induced nausea and vomiting in surgical patients· *abstract* **208P**

Patient preferences for immediate postoperative recovery **760**

Why does smoking protect against PONV? *editorial* **810**

Management of post-strabismus nausea and vomiting in children using ondansetron: a value-based comparison of outcomes **473**

Predictive models for postoperative nausea and vomiting: *correspondence* **339**

vomiting, nausea, anaesthetic factors, Comparison of morphine alone with morphine plus clonidine for postoperative patient-controlled analgesia **424**

BJA

British Journal of Anaesthesia

International Journal of Anaesthesia

Volume 89 · 2002

Editor-in-chief: Jennifer M. Hunter

Published by

OXFORD
UNIVERSITY PRESS

Printed in Great Britain by Information Press Ltd, Oxford

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

British Journal of Anaesthesia

CONTENTS

JULY

EDITORIAL

1 Molecular and basic mechanisms of anaesthesia
K. W. Miller, C. D. Richards, S. H. Roth and B. W. Urban

MOLECULAR AND BASIC MECHANISMS OF ANAESTHESIA

3 Concepts and correlations relevant to general anaesthesia
B. W. Urban and M. Bleckwenn
17 The nature of sites of general anaesthetic action
K. W. Miller
32 Molecular modelling of specific and non-specific anaesthetic interactions
J. R. Trudell and E. Bertaccini
41 The effects of general anaesthetics on ligand-gated ion channels
J. P. Dilger
52 Mechanisms of (local) anaesthetics on voltage-gated sodium and other ion channels
A. Scholz
62 Anaesthetic actions on other targets: protein kinase C and guanine nucleotide-binding proteins
M. J. Rebecchi and S. N. Pentyala
79 Anaesthetic modulation of synaptic transmission in the mammalian CNS
C. D. Richards
91 *In vitro* networks: subcortical mechanisms of anaesthetic action
J. J. Kendig
102 *In vitro* networks: cortical mechanisms of anaesthetic action
B. Antkowiak
112 *In vivo* imaging of anaesthetic action in humans: approaches with positron emission tomography (PET) and functional magnetic resonance imaging (fMRI)
W. Heinke and C. Schwarzbauer
123 What can *in vivo* electrophysiology in animal models tell us about mechanisms of anaesthesia?
C. Vahle-Hinz and O. Detsch
143 *In vivo* genetics of anaesthetic action
H. A. Nash
156 *In vivo* characterization of clinical anaesthesia and its components
J. F. Antognini and E. Carstens
167 Current assessment of targets and theories of anaesthesia
B. W. Urban

CORRESPONDENCE

184 Transtracheal high frequency jet ventilation and iatrogenic injury
184 Methods of post-thoracotomy analgesia
185 Prone, head down for pulmonary haemorrhage
186 Use of the Intubating Laryngeal Mask in failed intubation associated with amyloid macroglossia
187 Mobile operating theatre. Why must it be mobile?
187 Cuffed Portex tracheal tube
188 Pain and injury from epidural injection
188 Retroperitoneoscopic excision of phaeochromocytoma

BOOK REVIEWS

189 *Anesthesia and Neurosurgery*
190 *Critical Care Medicine: Principles of Diagnosis and Management in the Adult*
190 *Safe Retrieval and Transfer: the Practical Approach*
191 *Atlas of Hemofiltration*
191 *The Year in Hypertension 2001*
191 *Pediatric Anesthesia: Principles and Practice*
192 *Shnider and Levinson's Anesthesia for Obstetrics*
193 *Key Topics in Chronic Pain*

ABSTRACTS

194P Proceedings of the Anaesthetic Research Society Meeting, University of Sheffield, April 11–12, 2002

AUGUST

EDITORIALS

211 I. Management of casualties from terrorist chemical and biological attack: a key role for the anaesthetist
D. J. Baker
214 II. Blood transfusion in surgical practice—matching supply to demand
J. C. Howie and P. J. Tansey
216 III. Inflammation and the coagulation system
N. R. Webster

CLINICAL INVESTIGATIONS

221 Validation of a clinical prediction rule to reduce preoperative type and screen procedures
W. A. van Klei, K. G. M. Moons, A. T. Rheineck-Leyssius, C. J. Kalkman, C. L. G. Rutten, J. T. A. Knape and D. E. Grobbee
226 Effects on coagulation of intravenous crystalloid or colloid in patients undergoing peripheral vascular surgery
T. G. Ruttmann, M. F. M. James and J. Finlayson
231 Alveolar and serum oxidative stress in ventilator-associated pneumonia
F. Duflo, R. Debon, J. Goudable, D. Chassard and B. Allaouchiche
237 Comparison of oesophageal and gastric air tonometry in patients with circulatory failure
U. Janssens, H. Groesdonk, J. Graf, P. W. Radke, W. Lepper and P. Hanrath
242 Propofol attenuates myocardial lipid peroxidation during coronary artery bypass grafting surgery
M. M. Sayin, O. Özatamer, R. Taşöz, K. Kilinç and N. Unal
247 Exhaled nitric oxide as a marker of lung injury in coronary artery bypass surgery
B. H. Cuthbertson, S. A. Stott and N. R. Webster

251 Plasma concentration of ropivacaine after intercostal blocks for video-assisted thoracic surgery
H. Behnke, F. Worthmann, J. Cornelissen, M. Kahl and H. Wulf

254 Ultrasound-guided infraclavicular brachial plexus block
N. S. Sandhu and L. M. Capan

260 Changes in the rapidly extracted auditory evoked potentials index and the bispectral index during sedation induced by propofol or midazolam under epidural block
S. J. Ge, X. L. Zhuang, Y. T. Wang, Z. D. Wang and H. T. Li

265 Transient hyperaemic response to assess vascular reactivity of skin; effect of locally iontophoresed sodium nitroprusside
V. L. Webster and R. P. Mahajan

271 Maintenance of stable cuff pressure in the Brandt™ tracheal tube during anaesthesia with nitrous oxide
F. Karasawa, T. Okuda, T. Mori and T. Oshima

277 Optimal rocuronium dose for intubation during inhalation induction with sevoflurane in children
M. Eikermann, I. Hunkemöller, L. Peine, W. Armbruster, B. Stegen, J. Hüsing and J. Peters

LABORATORY INVESTIGATIONS

282 Expansion of air bubbles in aqueous solutions of nitrous oxide or xenon
G. Lockwood

287 Regional response of cerebral blood volume to graded hypoxic hypoxia in rat brain
C. Julien-Dolbec, I. Tropres, O. Montigon, H. Reutenauer, A. Ziegler, M. Decorps and J.-F. Payen

294 Differential effects of isoflurane on excitatory and inhibitory synaptic inputs to thalamic neurones *in vivo*
O. Detsch, E. Kochs, M. Siemers, B. Bromm and C. Vahle-Hinz

301 Effects of mild and moderate hypothermia on apoptosis in neuronal PC12 cells
T. Shibano, Y. Morimoto, O. Kemmotsu, H. Shikama, K. Hisano and Y. Hua

REVIEW ARTICLE

306 Chemical and biological weapons. Implications for anaesthesia and intensive care
S. M. White

SHORT COMMUNICATION

325 Auditory evoked response during propofol anaesthesia after pre-induction with midazolam
M. D. Brunner, M. R. Nel, R. Fernandes, C. Thornton and D. E. F. Newton

CASE REPORTS

328 Management of failed intubation in a septic parturient
D. Hinchliffe and A. Norris

331 High-dose tinzaparin in pregnancy and the need for urgent delivery
S. K. Backe and G. R. Lyons

335 CORRESPONDENCE

346 BOOK REVIEWS

349 ABSTRACTS
Proceedings of the Intensive Care Society and Riverside Group 'State of the Art' Meeting, London, December 17–18, 2001

SEPTEMBER

EDITORIALS

369 I. Confidential enquiries into maternal deaths, 1997–1999
G. M. Cooper, G. Lewis and J. Neilson

373 II. Pressure support ventilation and the critically ill patient with muscle weakness
J. W. H. Watt

CLINICAL INVESTIGATIONS

376 Impaired explicit memory after recovery from propofol/sufentanil anaesthesia is related to changes in the midlatency auditory evoked response
I. Rundshagen, K. Schnabel and J. Schulte am Esch

382 Effect of propofol anaesthesia on the event-related potential mismatch negativity and the auditory-evoked potential N1
T. P. Simpson, A. R. Manara, N. M. Kane, R. L. Barton, C. A. Rowlands and S. R. Butler

389 Prediction of the haemodynamic response to tracheal intubation: comparison of laser-Doppler skin vasomotor reflex and pulse wave reflex
M. Luginbühl, F. Reichlin, G. H. Sigurdsson, A. M. Zbinden and S. Petersen-Felix

398 Incidence and risk calculation of inotropic support in patients undergoing cardiac surgery with cardiopulmonary bypass using an automated anaesthesia record-keeping system
M. Müller, A. Junger, M. Brau, M. M Kwapisz, E. Schindler, H. Akinturk, M. Benson and G. Hempelmann

405 Delays in defibrillation: influence of different monitoring techniques
G. D. Perkins, C. Roberts and F. Gao

409 Effectiveness of acute postoperative pain management: I. Evidence from published data
S. J. Dolin, J. N. Cashman and J. M. Bland

424 Comparison of morphine alone with morphine plus clonidine for postoperative patient-controlled analgesia
S. A. Jeffs, J. E. Hall and S. Morris

428 Contribution of midazolam and its 1-hydroxy metabolite to preoperative sedation in children: a pharmacokinetic-pharmacodynamic analysis
T. N. Johnson, A. Rostami-Hodjegan, J. M. Goddard, M. S. Tanner and G. T. Tucker

438 Pharmacokinetics of 0.75% ropivacaine and 0.5% bupivacaine after ilioinguinal–iliohypogastric nerve block in children
T. I. Ala-Kokko, J. Karinen, E. Räihä, K. Kiviluoma and S. Alahuhta

442 Evaluation of S1 motor block to determine a safe, reliable test dose for epidural analgesia
Z. Daoud, R. E. Collis, B. Ateleanu and W. W. Mapleson

446 Effect of thoracic epidural anaesthesia on colonic blood flow
T. H. Gould, K. Grace, G. Thorne and M. Thomas

452 Comparison of intrathecal fentanyl and diamorphine in addition to bupivacaine for Caesarean section under spinal anaesthesia
C. M. Cowan, J. B. Kendall, P. M. Barclay and R. G. Wilkes

459 Patient-controlled epidural analgesia *versus* continuous infusion for labour analgesia: a meta-analysis
M. van der Vyver, S. Halpern and G. Joseph

466 Epidural analgesia and backache: a randomized controlled comparison with intramuscular meperidine for analgesia during labour
B. A. Loughnan, F. Carli, M. Romney, C. J. Doré and H. Gordon

473 Management of post-strabismus nausea and vomiting in children using ondansetron: a value-based comparison of outcomes
B. Sennaraj, D. Shende, S. Sadhasivam, S. Ilavajady and D. Jagan

LABORATORY INVESTIGATIONS

479 Effects of halothane and isoflurane on the contraction, relaxation and energetics of rat diaphragmatic muscle
B. Bouhemad, O. Langeron, G. Orliaguet, P. Coriat and B. Riou

486 Pharmacological preconditioning: comparison of desflurane, sevoflurane, isoflurane and halothane in rabbit myocardium
V. Piriou, P. Chiari, F. Lhuillier, O. Bastien, J. Loufoua, O. Raisky, J. S. David, M. Ovize and J.-J. Lehot

492 Role of propofol and its solvent, intralipid, in nitric oxide-induced peripheral vasodilatation in dogs
M.-F. Doursout, P. M. Joseph, Y. Y. Liang, C. J. Hartley and J. E. Chelly

REVIEW ARTICLE

499 Maternal deaths from anaesthesia. An extract from *Why Mothers Die 1997–1999*, the Confidential Enquiries into Maternal Deaths in the United Kingdom
T. A. Thomas and G. M. Cooper, on behalf of the Editorial Board of the Confidential Enquiries into Maternal Deaths in the United Kingdom

SHORT COMMUNICATION

509 Effect of a single dose of esmolol on the bispectral index scale (BIS) during propofol/fentanyl anaesthesia
H. Berkenstadt, R. Loebstein, I. Faibishenko, H. Halkin, I. Keidan and A. Perel

CASE REPORTS

512 Flow-by induced hypoventilation in high spinal cord lesions—report of two cases
S. Kannan, N. Sherwood and A. Armfield

514 Posterior spinal ligament rupture associated with laryngeal mask insertion in a patient with undisclosed unstable cervical spine
C. J. Edge, N. Hyman, V. Addy, P. Anslow, C. Kearns, R. Stacey and C. Waldmann

517 Complete airway obstruction in a ventilated patient after oesophageal dilatation
S. Francis, W. C. Russell and J. P. Thompson

519 Coronary artery spasm and non-Q-wave myocardial infarction following intravenous ephedrine in two healthy women under spinal anaesthesia
A. Wahl, F. R. Eberli, D. A. Thomson and M. Luginbühl

524 CORRESPONDENCE

530 BOOK REVIEWS

OCTOBER

EDITORIALS

535 I. Intraperitoneal administration of analgesia: is this practice of any utility?
A. Ng and G. Smith

537 II. Should we demand fresh red blood cells for perioperative and critically ill patients?
S. A. McLellan, T. S. Walsh and D. B. L. McClelland

CLINICAL INVESTIGATIONS

541 Comparison of two techniques for measuring penetration of sodium chloride particles through breathing system filters
A. R. Wilkes

546 Xenon has no effect on cytokine balance and adhesion molecule expression within an isolated cardiopulmonary bypass system
A. Bedi, W. T. McBride, M. A. Armstrong, J. M. Murray and J. P. H. Fee

551 Comparison of ocular microtremor and bispectral index during sevoflurane anaesthesia
L. G. Kevin, A. J. Cunningham and C. Bolger

556 Randomized, double-blind comparison of different inspired oxygen fractions during general anaesthesia for Caesarean section
W. D. Ngan Kee, K. S. Khaw, K. C. Ma, A. S. Y. Wong and B. B. Lee

562 Epinephrine and clonidine do not improve intrathecal sufentanil analgesia after total hip replacement
R. Fournier, E. Van Gessel, A. Weber and Z. Gamulin

567 Remifentanil compared with sufentanil during extra-corporeal shock wave lithotripsy with spontaneous ventilation: a double-blind, randomized study
H. Beloeil, G. Corsia, P. Coriat and B. Riou

571 Phenotyping malignant hyperthermia susceptibility by measuring halothane-induced changes in myoplasmic calcium concentration in cultured human skeletal muscle cells
T. Girard, S. Treves, K. Censier, C. R. Mueller, F. Zorzato and A. Urwyler

580 Pharmacodynamics of mivacurium chloride in 13- to 18-yr-old adolescents with thermal injury
J. A. J. Martyn, Y. Chang, N. G. Goudsouzian and S. S. Patel

586 Training course in local anaesthesia of the airway and fibreoptic intubation using course delegates as subjects
V. Patil, G. L. Barker, R. J. Harwood and N. M. Woodall

594 Evaluation of effects of magnesium sulphate in reducing intraoperative anaesthetic requirements
L. Telci, F. Esen, D. Akcora, T. Erden, A. T. Canbolat and K. Akpir

LABORATORY INVESTIGATIONS

599 Haemodynamic effects of an angiotensin-converting enzyme inhibitor and angiotensin receptor antagonist during hypovolaemia in the anaesthetized pig
F. Ryckwaert, P. Colson, E. André, P.-F. Perrigault, G. Guillon and C. Barberis

605 Apparent diffusion coefficient mapping predicts mortality and outcome in rats with intracerebral haemodynamic disturbance: potential role of intraoperative diffusion and perfusion weighted magnetic resonance imaging to detect cerebral ischaemia
S. Ishikawa, K. Yokoyama, T. Kuroiwa and K. Makita

614 Mechanisms of action of midazolam on expression of contextual fear in rats
L. Pain, A. Launoy, N. Fouquet and P. Oberling

REVIEW ARTICLE

622 Pathophysiology and clinical implications of perioperative fluid excess
K. Holte, N. E. Sharrock and H. Kehlet

SHORT COMMUNICATIONS

633 Root-cause analysis of an airway filter occlusion: a way to improve the reliability of the respiratory circuit
P. Garnerin, E. Schiffer, E. Van Gessel and F. Clergue

635 Saliva cyclic GMP increases during anaesthesia
T. Engelhardt, H. F. Galley, F. M. MacLennan and N. R. Webster

637 Remifentanil or propofol for sedation during carotid endarterectomy under cervical plexus block
H. Krenn, E. Deusch, H. Jellinek, W. Oczenski and R. D. Fitzgerald

CASE REPORTS

641 Spontaneous breathing combined with high frequency ventilation during bronchoscopic resection of a large tracheal tumour
M. Satoh, Y. Hirabayashi and N. Seo

644 Postoperative use of a cough-assist device in avoiding prolonged intubation
W. A. Marchant and R. Fox

647 Bilateral pleural effusions: unexpected complication after left internal jugular venous catheterization for total parenteral nutrition
H. G. W. Paw

650 The stuck central venous catheter: beware of potential hazards
S. Mahadeva, A. Cohen and M. Bellamy

652 Use of implantable cardioverter defibrillator and anti-arrhythmic agents in a parturient
A. J. Olufolabi, G. A. Charlton, S. A. Allen, I. M. Mettam and P. R. Roberts

655 Anaesthetic management of severe bradycardia during general anaesthesia using temporary cardiac pacing
V. Toprak, A. Yentur and M. Sakarya

658 CORRESPONDENCE

664 BOOK REVIEWS

669 ERRATUM

ABSTRACTS

670P Proceedings of the Anaesthetic Research Society Meeting, Cardiff Meeting, July 11–12, 2002

NOVEMBER

EDITORIAL

683 I. Live and let die? A structured approach to decision-making about resuscitation
P. Levack

CLINICAL INVESTIGATIONS

687 Cerebral haemodynamics in pregnancy and pre-eclampsia as assessed by transcranial Doppler ultrasonography
R. W. Sherman, R. A. Bowie, M. M. E. Henfrey, R. P. Mahajan and D. Bogod

693 Fluoride excretion in children after sevoflurane anaesthesia
C. Lejus, C. Le Roux, E. Legendre, M. Renaudin, H. L. Boiteau and M. Pinaud

697 Is morphine-induced sedation synonymous with analgesia during intravenous morphine titration?
X. Paqueron, A. Lumbroso, P. Mergoni, F. Aubrun, O. Langeron, P. Coriat and B. Riou

702 Spinal anaesthesia: comparison of plain ropivacaine 5 mg ml^{-1} with bupivacaine 5 mg ml^{-1} for major orthopaedic surgery
D. A. McNamee, A. M. McClelland, S. Scott, K. R. Milligan, L. Westman and U. Gustafsson

707 Paediatric regional anaesthesia, a survey of practice in the United Kingdom
J. C. Sanders

711 Efficacy of intravenous magnesium in neuropathic pain
S. Brill, P. M. Sedgwick, W. Hamann and P. P. di Vadi

715 Platelet function point-of-care tests in post-bypass cardiac surgery: are they relevant?
F. Forestier, A. Coiffic, C. Mouton, D. Ekouevi, G. Chêne and G. Janvier

722 Effects of a new modified, balanced hydroxyethyl starch preparation (Hextend®) on measures of coagulation
J. Boldt, G. Haisch, S. Suttner, B. Kumle and A. Schellhaass

729 The laryngeal tube compared with the laryngeal mask: insertion, gas leak pressure and gastric insufflation
T. Asai, A. Kawashima, I. Hidaka and S. Kawachi

733 Fibreoptic tracheal intubation after placement of the laryngeal tube
H. V. Genzwuerker, T. Vollmer and K. Ellinger

LABORATORY INVESTIGATION

739 Neuroprotective and neurotoxic properties of the 'inert' gas, xenon
D. Ma, S. Wilhelm, M. Maze and N. P. Franks

REVIEW ARTICLE

747 Preoperative evaluation of patients with, or at risk of, coronary artery disease undergoing non-cardiac surgery
P.-G. Chassot, A. Delabays and D. R. Spahn

SHORT COMMUNICATIONS

760 Patient preferences for immediate postoperative recovery
L. H. J. Eberhart, A. M. Morin, H. Wulf and G. Geldner

762 Effect of diclofenac on cerebral blood flow velocity in patients with supratentorial tumours
S. J. Jones and J. Dinsmore

764 Sevoflurane and propofol decrease intraocular pressure equally during non-ophthalmic surgery and recovery
S. Sator-Katzenschlager, E. Deusch, S. Dolezal, A. Michalek-Sauberer, R. Grubmüller, G. Heinze and A. Wedrich
766 Atracurium is associated with postoperative residual curarization
C. McCaul, É. Tobin, J. F. Boylan and A. J. McShane
769 Effects of prolonged head-down tilt on internal jugular vein cross-sectional area
S. J. Schreiber, U. K. W. Lambert, F. Doepp and J. M. Valdueza
772 Posture used by anaesthetists during laryngoscopy
J. D. Walker

CASE REPORTS

775 Air embolism: diagnosis with single-photon emission tomography and successful hyperbaric oxygen therapy
L. Droghetti, M. Giganti, A. Memmo and R. Zatelli
778 Epidural abscess complicating insertion of epidural catheters
J. M. G. Phillips, J. C. Stedeford, E. Hartsilver and C. Roberts
782 Unexplained fitting in three parturients suffering from postdural puncture headache
C. D. Oliver, S. A. White
786 Anaesthesia in an adult with Rubenstein–Taybi syndrome using the ProSeal laryngeal mask airway
S. J. Twigg and T. M. Cook
788 General anaesthesia in a patient with Brugada syndrome
C. J. Edge, D. J. Blackman, K. Gupta and M. Sainsbury

COMMENTARY

792 Preoperative use of herbal medicines: a patient survey
C. M. Skinner and J. Rangasami

796 CORRESPONDENCE

802 BOOK REVIEWS

DECEMBER

EDITORIALS

807 I. Confidence in statistical analysis
T. Asai
810 II. Why does smoking protect against PONV?
B. P. Sweeney

CLINICAL INVESTIGATIONS

814 Phase behaviour of premixed 0.25% isoflurane in 50% nitrous oxide and 50% oxygen
M. E. Tunstall and J. A. Ross
820 Simulated use of premixed 0.25% isoflurane in 50% nitrous oxide and 50% oxygen
J. A. Ross and M. E. Tunstall
825 Equipment problems during anaesthesia—are they a quality problem?
S. Fasting and S. E. Gisvold
832 Stereoselective *in vitro* degradation pattern of mivacurium in human plasma
J. Laurin, F. Donati and F. Varin
839 Pharmacogenetics of codeine metabolism in an urban population of children and its implications for analgesic reliability
D. G. Williams, A. Patel and R. F. Howard
846 Plasma lidocaine concentrations following insertion of 2% lidocaine gel into the uterine cavity after uterine balloon thermal ablation
G. F. Rousseau, M. Oram, J. Barrington, M. Priston and M. Swart
849 Effects of intramuscular administration of lidocaine or bupivacaine on induction and maintenance doses of propofol evaluated by bispectral index
M. Senturk, K. Pembeci, F. Menda, T. Ozkan, B. Gucyetmez, M. Tugrul, E. Camci and K. Akpir
853 Sevoflurane anaesthesia in children after induction of anaesthesia with midazolam and thiopental does not cause epileptiform EEG
K. Nieminen, S. Westerèn-Punnonen, H. Kokki, H. Yppärilä, A. Hyvärinen and J. Partanen
857 Esmolol prevents movement and attenuates the BIS response to orotracheal intubation
C. Menigaux, B. Guignard, F. Adam, D. I. Sessler, V. Joly and M. Chauvin
863 Patient satisfaction with anaesthesia care: development of a psychometric questionnaire and benchmarking among six hospitals in Switzerland and Austria
T. Heidegger, Y. Husemann, M. Nuebling, D. Morf, T. Sieber, A. Huth, R. Germann, P. Innerhofer, A. Faserl, C. Schubert, C. Geibinger, K. Flückiger, T. Coi and G. Kreienbühl
873 Stress in UK intensive care unit doctors
S. Coomber, C. Todd, G. Park, P. Baxter, J. Firth-Cozens and S. Shore

LABORATORY INVESTIGATIONS

882 Comparison of effects of anandamide at recombinant and endogenous rat vanilloid receptors
J. C. Jerman, J. Gray, S. J. Brough, L. Ooi, D. Owen, J. B. Davis and D. Smart
888 Electrophysiological effects of morphine in an *in vitro* model of the ‘border zone’ between normal and ischaemic–reperfused guinea-pig myocardium
A. Yvon, J.-L. Hanouz, X. Terrien, P. Ducouret, R. Rouet, H. Bricard and J.-L. Gérard

896 Sevoflurane preconditions stunned myocardium in septic but not healthy isolated rat hearts
R. Serita, H. Morisaki, K. Ai, Y. Morita, Y. Innami, T. Satoh, S. Kosugi, Y. Kotake and J. Takeda

REVIEW ARTICLE

904 Parkinson's disease and anaesthesia
G. Nicholson, A. C. Pereira and G. M. Hall

SHORT COMMUNICATIONS

917 What information do anaesthetists provide for patients?
G. M. M. Thoms, G. A. McHugh and J. A. Lack

919 Lactic acidosis in the rectal lumen of patients with septic shock measured by luminal equilibrium dialysis
V. Due, J. Bonde, K. Espersen, T. H. Jensen and A. Perner

922 Bacterial contamination of epidural needles after multiple skin passes
C. Orlikowski, P. M. Majedi and A. D. Keil

CASE REPORTS

925 Intrathecal morphine overdose during combined spinal–epidural block for Caesarean delivery
M. Cannesson, N. Nargues, B. Bryssine, R. Debon, E. Boselli and D. Chassard

927 Management of a known difficult airway in a morbidly obese patient with gross supraglottic oedema secondary to thyroid disease
M. Hariprasad and G. J. Smurthwaite

930 Probable allergic reaction to cyclosporin and early formation of thrombi on a pulmonary artery catheter: two unusual complications during bilateral lung transplantation
N. Dalibon, M. Stern, P. Bonnette, G. Dreyfus and M. Fischler

934 CORRESPONDENCE

940 BOOK REVIEWS

945 INDEX TO VOLUME 89

Guide to Contributors

The purpose of the *British Journal of Anaesthesia* is the publication of original work in all branches of anaesthesia, including the application of basic sciences. One issue each year deals mainly with material of postgraduate educational value.

Papers for publication and all editorial communications should be addressed to: Professor J. M. Hunter, Editor-in-Chief, *British Journal of Anaesthesia*, University Department of Anaesthesia, Royal Liverpool University Hospital, The Duncan Building, Daulby Street, Liverpool L69 3GA, UK. Tel./Fax: +44 (0) 151 706 4005. E-mail: bja@liv.ac.uk

Papers

Papers submitted must not have been published in whole or in part in any other journal, and are subject to editorial revision. It is a condition of acceptance for publication that copyright becomes vested in the journal and permission to republish must be obtained from the publisher.

Papers based on clinical investigation should conform to ethical standards as set out in the Declaration of Helsinki and should normally include a statement of approval from an appropriate Ethics Committee. In the case of animal studies it is the responsibility of the author to satisfy the Board that no unnecessary suffering has been inflicted. Studies from the UK should specify the Home Office Licence number; from elsewhere, a statement of approval from an appropriate licensing authority.

Legal considerations

Authors should avoid the use of names, initials and hospital numbers which might lead to recognition of a patient. A patient must not be recognizable in photographs unless written consent of the subject has been obtained. A table or illustration that has been published elsewhere should be accompanied by a statement that permission for reproduction has been obtained from the authors and publishers.

Preparation of manuscript

Four copies of each manuscript (including revised texts) should be submitted and should indicate the title of the paper, the name(s), full address(es) of the author(s), and be in letter quality heavy type (not dot matrix), double-spaced on one side only of the paper, with a wide margin. Contributors should retain a copy in order to check proofs and in case of loss. Where possible, manuscripts should also be submitted on disk. Our preferred format is a 3.5″ PC floppy disk with the file written in Word 6 for Windows. However, it is also possible to process disks submitted in other formats, provided sufficient information is supplied to enable conversion to the preferred format. Articles on disk should be prepared in the simplest possible form. Please do not use endnotes, footnotes, etc. for references. Correct fonts, type sizes, column measures, etc, will be added by the technical editor.

Each of the four copies submitted must be accompanied by a complete set of figures. One set of figures must be unmounted glossy prints (see below); the three other sets may be photocopies.

Manuscripts should be accompanied by a formal letter of request for publication which should be signed by all the authors. There should be a clear declaration of any financial or commercial interest which any author may have in the material. The Editor may wish to see raw data if necessary.

Papers in recent issues of *British Journal of Anaesthesia* should be consulted for general and detailed presentation. They are most often subdivided into:

Title page
Summary, including Keywords
Introduction (not headed)
Methods
Results
Discussion
Acknowledgements
List of references
Tables (including legends to tables)
Illustrations (including captions)

Title page

There should be a separate title page, including the name(s) and address(es) of all author(s). It should be made clear which address relates to which author. Authors' present addresses differing from those at which the work was carried out, or special instructions concerning the address for correspondence, should be given and referenced at the appropriate place in the author list by superscript numbers. If the address to which proofs should be sent is not that of the first-mentioned author, clear instructions should be given in a covering note and not on the title page. The title page should be paginated as page 1 of the paper.

A short running title containing not more than 50 characters and spacing should be included.

Summary

The summary will be printed at the beginning of the paper. It should be on a separate sheet, in structured format (Background; Methods; Results; and Conclusions) for all original articles (Clinical Investigations, Laboratory

© The Board of Management and Trustees of the British Journal of Anaesthesia 2002

Investigations, and Short Communications) but not for Reviews, Case Reports, or Commentaries. It should give a succinct account of the problem, in up to 250 words. It may be used as it stands by abstracting journals. References are not used in this section, except in exceptional circumstances.

Three to five key words or phrases (for indexing) should be included below the summary.

Introduction

The introduction should give a concise account of the background of the problem and the object of the investigation. Previous work should be quoted only if it has a direct bearing on the present problem.

Methods

Methods must be described in sufficient detail to allow the investigation to be interpreted and repeated by the reader. Any modification of previously published methods should be described and the reference given. If the methods are commonly used, only a reference to the original source is required.

Drugs

When a drug is first mentioned it should be given the international non-proprietary name, followed in parentheses by the chemical formula only if the structure is not well known, and by the capitalized proprietary name.

Results

Description of results, while concise, should permit repetition of the investigation by others. Data should not be repeated unnecessarily in text, tables and figures, and unwarranted numbers of digits should be avoided. Significance should be given as values of probability.

Discussion

The discussion should not merely recapitulate the results, but should present their interpretation against the background of existing knowledge. It should include a statement of any assumptions on which conclusions are based.

Acknowledgements

Acknowledgements will be printed in small type. They should be brief, and should include reference to sources of support and sources of drugs not freely available commercially. Individuals named must be given the opportunity to read the paper and approve their inclusion in the acknowledgements, before the paper is submitted.

References

There should be a list of references at the conclusion of the paper, commencing on a new sheet.

References must be numbered consecutively in the order in which they are first mentioned in the text, with the exception of review articles, when references should be arranged alphabetically.

References in text, tables and legend should be identified by arabic numbers appearing in the text in superscript, for example [5] or [5–7] or [5 16] for unrelated references. When a table or figure is first mentioned, its reference must continue the sequence.

Use the style of references adopted by the US National Library of Medicine and used in *Index Medicus.* The titles of journals should be abbreviated.

The names and initials of more than six authors should be abbreviated to three authors followed by *et al.*

Text references to 'unpublished observations' or 'personal communications' should not be included in the final list of references. Authors are responsible for verifying that the wording of references to unpublished work is approved by the persons concerned. Papers which have been submitted and accepted for publication should be included in the list, the phrase 'in press' replacing volume and page number. Information from manuscripts submitted but not yet accepted should be cited in the text as unpublished observations.

Examples of correct forms of references:

Journals:

1. Brown BR jr, Gandolphi AJ. Adverse effects of volatile anaesthetics *Br J Anaesth* 1987; **59**: 14-23

Chapter in a book:

2. Hull CJ Opioid infusions for the management of postoperative pain. In: Smith G, Covino BG, eds. *Acute Pain.* London. Butterworths, 1985; 155-79

Monographs:

3. Moore, DC *Regional Block,* 4th Edn. Springfield, Illinois: Charles C. Thomas, 1979

Restrict references to those that have direct bearing on the work described and cite only references to books and articles published in *Index Medicus* journals.

It is essential that authors verify the content and detail of references which they list against the original articles, as this responsibility cannot be accepted by either Editors or publishers.

Tables

All tables should be on separate sheets and be capable, with their captions, of interpretation without reference to the text. They should be numbered consecutively with Arabic numerals. Units in which results are expressed should be given in brackets at the top of each column, and not repeated on each line of the table. Ditto signs are not used. Footnotes are not used.

Illustrations

Photographs should be unmounted glossy prints, and should be protected adequately for mailing. Surfaces should not

be marred with clips, pins or by heavy writing on the back. Drawings, charts and graphs should be in black indict ink on white paper and, if in sets, should be presented at a uniform magnification. Illustrations should be clearly numbered on the back, preferably in soft pencil, with reference to the text, and using Arabic numbers. They should be accompanied on a separate sheet by a suitable legend. Lettering should be professional-looking, uniform, preferably in a common typeface, large enough to read at a reduced size, and in proportion to the illustrated material. Lines in the original must also be thick enough to allow for reduction. Magnifications, especially in photomicrographs, should be indicated by a scale on the photograph itself, in order to remain appropriate after reduction. Symbols which are to appear in the figure (and not in the legend) should be chosen from the following available types:

● ○ ■ □ ▼ ▽ ▲ △ ◆ ◇ × +

The names of the author and title of the paper should also be written in soft pencil on the back of the illustrations.

It should be noted that A4-size figures generated by computer are usually unacceptable (see Extended Guide to Contributors—*Br J Anaesth* 2000; **84**: 131-7).

General information

Instructions to the printer. Words to be printed in lowercase italics should be indicated by one underline. Two underlines indicate small capitals, three indicate large capitals and four, italic capitals. A wavy underline indicates a word to be printed in bold type.

Headings in the text. Three possible grades are available, and may be indicated by the following letters of identification.

A **Results (bold)**
B *Lung function studies* (italics, ranged left)
C *Volume.* Large volumes . . . (italics, ranged left, text run on)

Symbols and abbreviations. In accordance with Editorial adoption of SI units, abbreviations and symbols should follow the conventions described in the booklet *Units, Symbols and Abbreviations. A Guide for Biological and Medical Editors and Authors* (D. N. Baron, ed.) (1988), published by and available from The Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE. Words for which abbreviations are not included should be written in full at first mention in the summary and again in the text and followed by the abbreviation in brackets. This will usually be in the form of large capitals without separating points.

Spelling, etc. British spelling should be used with 'z' rather than 's' spelling in, e.g. organize, organization.

Short communications

Authors are encouraged to submit short manuscripts suitable for rapid publication. In general, these should conform to the requirements outlined above, but with the following differences:

Format. Summary; Introduction (not headed); Methods and results; Comment.

Size. Not more than 6 references, 1 table or 1 figure, one-and-a-half pages of printed text (1200 words).

Correspondence

Each issue of the journal will contain correspondence. Correspondence arising from papers in a recent issue is published without delay, and for this reason, will be given priority over that pertaining to original research. The Editor may change, delete or modify in any way all items of correspondence.

All communications designed for publication should be submitted on a separate page in letter quality heavy type (not dot matrix), double-spaced, on one side only of the paper, with a wide margin. Contributors should send three copies of all correspondence to the editor and retain a copy in case of loss. Correspondence must also be submitted on disk. All authors must sign the accompanying submission letter. A fax number and an E-mail address should be supplied.

Proofs

These should be corrected and returned to the publisher by post or fax within 48 h of receipt. Overseas contributors may fax a copy of the proofs to the publisher but should return their proofs by air mail also.

Reprints

Corresponding authors will receive a copy of the journal in which their article appears. Offprints can be supplied if application is made on the order form attached to the proofs. The order form should be returned with the proofs.

IMPORTANT NOTICE TO AUTHORS

Electronic submission of new manuscripts to the British Journal of Anaesthesia. Please note that, from January 2003, the Editorial team requests that all new manuscripts (excluding Letters to the Editor and Book Reviews), be submitted electronically to the *British Journal of Anaesthesia* web site at: http://bja.manuscriptcentral.com

Clear instructions for submission of new manuscripts are available on this web site. If these instructions are not adhered to, difficulty will be experienced in submitting new articles. For an interim period, manuscripts may also be submitted as hard copy to the Editor-in-Chief's office. It is envisaged, however, that this arrangement will be discontinued by the end of 2003.

ANESTHESIA & ANALGESIA

Journal of the International Anesthesia Research Society, the Society of Cardiovascular Anesthesiologists, the Society for Pediatric Anesthesia, the Society for Ambulatory Anesthesia, the International Society for Anaesthetic Pharmacology, and the Society for Technology in Anesthesia

EDITORIAL

1131 Lidocaine for Neuroprotection: More Evidence of Efficacy

CARDIOVASCULAR ANESTHESIA (Society of Cardiovascular Anesthesiologists)

1134 Lidocaine and Cognitive Dysfunction
1142 Off-Pump Coronary Artery Bypass Graft and Patent Foramen Ovale
1147 Anesthetics, Defibrillation Energy Threshold and Human Implantable Cardioverter Defibrillator
1154 Isovolemic Versus Hypervolemic Hemodilution
1162 Isoflurane and Second Window of Preconditioning
1169 The Effect of Donor Hypernatremia in Rat Orthotopic Liver Transplantation
1173 Hemodynamic and Hormonal Responses to Hepatic Vascular Exclusion
1179 Epidural Analgesia and Liver Resection (Brief Report)
1182 Noninvasive Indocyanine Green Elimination (Case Report)
1185 Ureteral Stent and Pulmonary Embolism (Case Report)
1189 Bronchial Stenting and Persistent Atelectasis (Case Report)
1192 Arterial Line Cable Corrosion Artifact (Case Report)
1196 Supine Hypertension with Midodrine (Case Report)
1198 Aortic Valve Fibroelastomas and TEE (Case Report)

PEDIATRIC ANESTHESIA (Society for Pediatric Anesthesia)

1200 Pulmonary-to-Systemic Blood Flow Ratio in Congenital Heart Surgery
1207 Intrathecal Versus IV Fentanyl in Pediatric Cardiac Surgery
1215 Caudal Neostigmine
1219 Caudal Anesthesia Volume Versus Concentration
1224 FLACC Pain Assessment in Children with Cognitive Impairment
1230 Posttonsillectomy Vomiting
1236 Laparoscopy and Portal Hypertension
1241 New Approach for One-Lung Ventilation (Case Report)
1243 Laparoscopic Adrenalectomy (Case Report)
1245 Tension Pneumopericardium in an Infant (Case Report)
1248 Vallecular Cyst with Laryngomalacia (Case Report)
1251 Bilateral Pneumothoraces (Case Report)

AMBULATORY ANESTHESIA (Society for Ambulatory Anesthesia)

1253 Lidocaine Versus Ropivacaine in Anorectal Surgery

ANESTHETIC PHARMACOLOGY (International Society for Anaesthetic Pharmacology)

1258 Pain After Day Surgery and General Practitioners' Views (Special Article)
1263 Glutamate Transporter EAAT3, Lidocaine, Protein Kinase C, and P13K
1269 Inhibitory Effect of Tramadol on M_3 Receptor
1274 Anesthetics and Norepinephrine Release
1282 Changes in Cerebrospinal Fluid Propofol Concentration During Target-Controlled Infusion
1285 Propofol Phosphate-Propofol Prodrug
1293 Ephedrine Reduces Propofol-Induced Pain

TECHNOLOGY, COMPUTING, AND SIMULATION (Society for Technology in Anesthesia)

1297 Diazepam, Pain Injection and Lidocaine or Metoclopramide
1300 Analgesic Effect of Xenon
1305 In Vitro Metabolism of Remifentanil
1308 Rofecoxib and ENT Surgery
1312 Modeling of Cell Salvage
1318 Auditory Steady State Response as Anesthesia Monitor?
1324 EEG and Remifentanil/Propofol Anesthesia
1331 Infusion Pump Delivery Rate Accuracy
1337 Dermatitis with Use of BIS Monitor (Case Report)

PAIN MEDICINE

1339 Guanethidine and Local Anesthetics
1344 Ropivacaine for Postthoracotomy Analgesia
1351 Preemptive Analgesia by Suppression of Postoperative Pain
1358 Venous Malformation and Pain (Case Report)
1361 Acute Pain Service and Outcome (Review Article)

ECONOMICS, EDUCATION, AND HEALTH SYSTEMS RESEARCH

1373 Therapeutic and Diagnostic Interventions and Scoring System
1381 Preoperative Assessment of Hypothermia

NEUROSURGICAL ANESTHESIA

1384 Sevoflurane Versus Isoflurane in Neurosurgery
1389 Paraparesis by Morphine and GABA Drugs

OBSTETRIC ANESTHESIA

1396 Subarachnoid Clonidine in Labor

REGIONAL ANESTHESIA

1402 Epinephrine and Systemic Absorption of Epidural Ropivacaine
1408 Test Dose and Electrocardiogram
1412 Epidural Block and Operative Isoflurane Dosage
1419 Intravenous Regional Anesthesia Using Prilocaine and Neostigmine
1423 Assessment of Teaching Model
1428 Lumbar Plexus Posterior Approach and Catheter Placement (Brief Report)

GENERAL ARTICLES

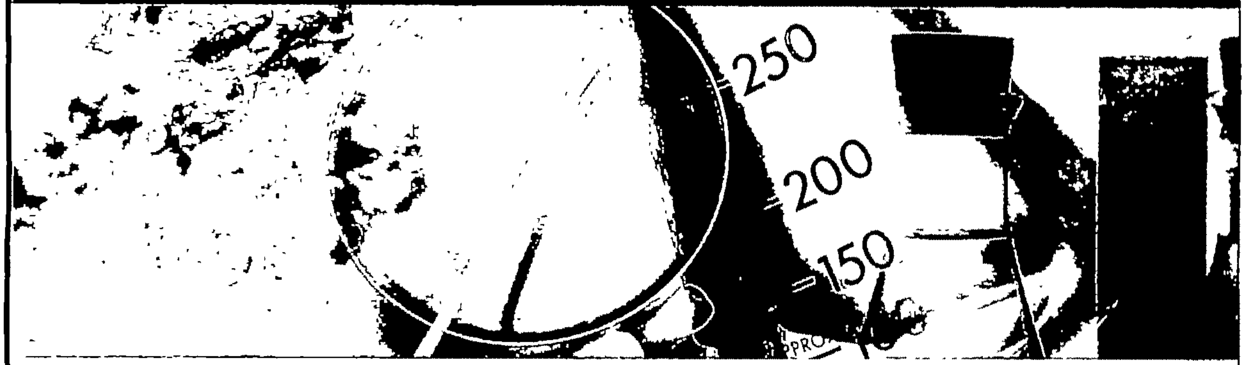
1432 Nasotracheal Intubation Technique
1437 Reliability Of Bellhouse Test
1442 Postoperative Antiemetic Effects of Tandospirone
1446 Influences on Postoperative Fatigue
1451 Postoperative Lateral Medullary Syndrome (Case Report)
1454 Intubating Laryngeal Mask Airway for Fixed Flexed Neck (Case Report)
1459 LETTERS TO THE EDITOR
1468 BOOK AND MULTIMEDIA REVIEWS

STA PRECONVENTION ISSUE

SEE INFORMATION INSIDE

ISSN 0003-2999 Volume 95, Number 5, November 2002
www.anesthesia-analgesia.org

OXFORD JOURNALS



QJM - An International Journal of Medicine

Editor: Dr. Christopher N. Martyn

www.qjmed.oupjournals.org/?f2

QJM is a long-established, leading general medical journal. It focuses on internal medicine and publishes peer-reviewed articles which promote medical science and practice.

7 reasons to publish in QJM

1 Impact factor of 2.25
2 Rapid publication - about 10 weeks post acceptance
3 Opportunity for in-depth articles and reviews
4 Influential readership that includes a wide range of specialists
5 Online manuscript submissions from 2002 - e-mail submissions already accepted
6 Wide usage of QJM online and extensive links ensure a high profile for all papers
7 Inclusion in all major indexing/abstracting services

➲ **FULL TEXT** *now online*

If you are a current print subscriber (institutional or personal), visit **www3.oup.co.uk/Register/?f2** to activate your online access.

➲ **FREE @ the web site:**

- tables of contents by e-mail
- sample issue
- abstracts and tables of contents
- instructions to authors

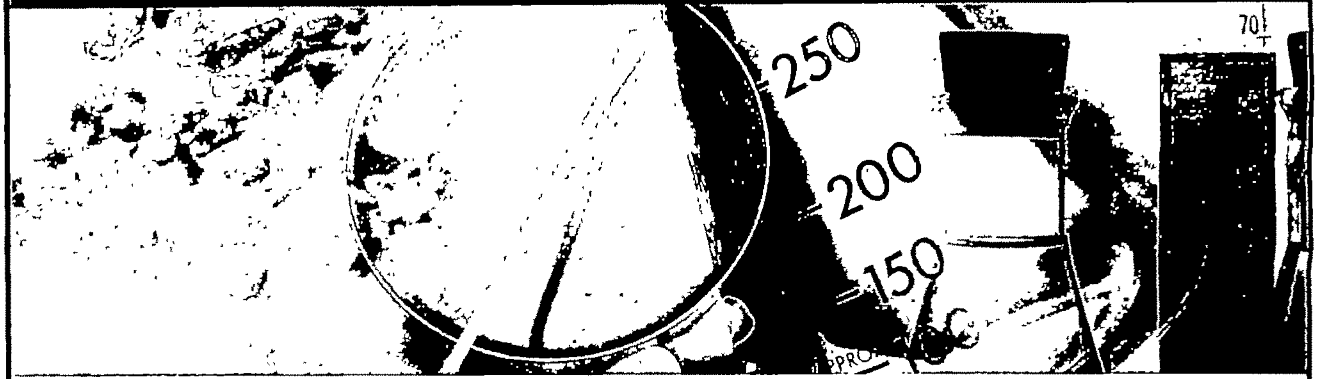
To subscribe, visit the web site @
www.qjmed.oupjournals.org/?f2

For further information please contact:
Journals Dept. • E-mail jnls cust serv@oup co.uk
Tel: +44 1865 267907 • Fax: +44 1865 267835

In the Americas, please contact:
Journals Dept. • E-mail· jnlorders@oup-usa org
Tel: +1 800 852 7323 (USA/Canada) or +1 919 677 0977
(outside USA/Canada) • Fax: +1 919 677 1714

OXFORD
UNIVERSITY PRESS

OXFORD JOURNALS



BJA CEPD Reviews

www.oupjournals.org/list/bjarev/?f2

Editor-in-Chief: David J Rowbotham

BJA CEPD Reviews is a joint venture of the British Journal of Anaesthesia and The Royal College of Anaesthetists in collaboration with the Intensive Care Society and Pain Society.

The purpose of ***BJA CEPD Reviews*** is the publication of material to support the continuous medical education and professional development of specialists in anaesthesia, critical care medicine and pain

To subscribe, visit the web site @
www.oupjournals.org/list/bjarev/?f2

For further information please contact:
Journals Dept. • E-mail: jnls.cust.serv@oup.co.uk
Tel: +44 1865 267907 • Fax: +44 1865 267835
In the Americas, please contact:
Journals Dept • E-mail: jnlorders@oup-usa.org
Tel: +1 800 852 7323 (USA/Canada) or +1 919 677 0977
(outside USA/Canada) • Fax: +1 919 677 1714

OXFORD
UNIVERSITY PRESS

Washington
University in St. Louis
SCHOOL OF MEDICINE

CHIEF OF NEUROLOGIC ANESTHESIA

The Department of Anesthesiology at Washington University School of Medicine is seeking an experienced academic anesthesiologist to head the Section of Neurologic Anesthesia and direct the clinical and academic activities of the service. The service provides anesthesia coverage for approximately 1,600 cases per year. A strong multidisciplinary integrated approach with the neurosurgery, neuroradiology and neurointensive care services is already established. The infrastructure for clinical and outcome research is in place. The faculty appointment is at the rank of Associate Professor or Professor and is commensurate with the candidate's credentials. Salary and benefits are competitive. Candidates interested in this position should send their CV to.

René Tempelhoff, MD
Chair of Search Committee
Department of Anesthesiology
Washington University School of Medicine
660 S. Euclid Avenue, Campus Box 8054
St. Louis, MO 63110.
Telephone: (314) 362-2330
E-mail: tempelhr@msnotes.wustl.edu.

The University of Iowa Department of Anesthesia
Faculty Position: Human Patient Simulator Director

The University of Iowa, Department of Anesthesia is actively recruiting an outstanding clinician and educator for a leadership role in our department through leadership of our human patient simulator program We are interested in candidates with a desire to direct and develop our human patient simulator education suite as a means of educating our medical students, physician residents, and other professionals in a unique and challenging ways We are looking for candidates to be appointed to either our tenure or non-tenure clinical track in any of our academic ranks.

The Department is interested in anesthesiologists interested in working in a collegial setting where research, clinical care and education are all valued. The University of Iowa is located in Iowa City, a vibrant community located in the rolling hills of southeastern Iowa. The community offers excellent schools, quality entertainment, literary, musical and cultural opportunities and Big-10 sporting events Please send CV and contact:

David L Brown, M.D., Professor and Head
Department of Anesthesia, The University of Iowa
200 Hawkins Drive, Room 6618 JCP
Iowa City, Iowa 52242-1079
Telephone (319) 356-2382 or Fax (319) 356-4130

The University of Iowa is an Affirmative Action and Equal Opportunity Employer. Women and minorities are strongly encouraged to apply.

The Neuroanaesthesia Society
Of Great Britain and Ireland
Annual Update and Scientific Meeting
Manchester

April 3rd-4th 2003

At the
Manchester Conference Centre

Debate on topical issues. Educational Update
Guest Speakers. Panel Discussions
Free papers. Anaesthetists in training eligible for prizes
Deadline for abstracts: 21st February 2003

This meeting attracts 10 CEPD points

Information & registration form at:
www.nasgbi.org.uk
Register online at:
www.meeting.co.uk/nasman2003
More information from:
Manchester Conference Centre,
UMIST, PO Box 88,
Manchester, M60 1QD. UK.
Tel: 0161 200 4068

14th South West Thames
Anaesthesia Update

27-31 January 2003
Belle Plagne, French Alps

Open to all Anaesthetists
The Scientific Programme will include lectures, and discussions on:

- Acute and Chronic Pain
- Paediatric Update
- Day Case Anaesthesia
- Obstetric Anaesthesia
- Neurology and Anaesthesia
- ITU and Relevant Medical Topics
- Cardiothoracic topics
- Radiology for Anaesthetist
- New Drugs Update
- Training &Education
- Anaesthetic Audit
- Free papers
- Panel Discussions
- Workshops

Guest Speakers
Videos on New Equipment, Drugs and Techniques
Anaesthetists in training presenting papers are eligible for prizes
Deadline for abstracts: December 9th 2002
This Meeting is approved for CME purposes

For further details, please contact:
Dr J.B. Liban
Department of Anaesthesia
St George's Hospital
Blackshaw Road,
London SW17 0QT
Fax: +44 (0)20 8725 3135
Tel: +44 (0)20 8725 0018
email: liban@mailbox.co.uk

www.doctorsupdates.com
medical education in a perfect location

Dunedin, New Zealand

Ritchie Professor in Anaesthesia

(Fixed-term)

UNIVERSITY of OTAGO

Te Whare Wānanga o Otāgo

Section of Anaesthesia and Intensive Care, Department of Medical and Surgical Sciences,
Dunedin School of Medicine
and Otago District Health Board

The Dunedin School of Medicine, in association with the Otago District Health Board, seeks to appoint a Professor in Anaesthesia. This is a newly created position intended to re-establish a strong academic and research presence in Anaesthesia, Intensive Care and Pain Management within the Dunedin School of Medicine.

This Chair, based in Dunedin Hospital, becomes available for a fixed-term of five years from 1 January 2003. We seek a specialist Anaesthetist, who holds, or is eligible for, vocational registration in New Zealand. The appointee is expected to possess excellent organisational and leadership qualities, the potential to develop a high quality research and teaching programme and a record of achievement in these areas. The appointee is expected to undertake clinical responsibilities in Anaesthesia in addition to the designated academic roles.

Further information is available from the Professor R J Walker, Department of Medical and Surgical Sciences, Dunedin School of Medicine, Tel 64 3 474 0999, Fax 64 3 474 7641, Email medsurg@stonebow.otago.ac.nz or from the Director of Anaesthesia, Email geoff.laney@stonebow.otago.ac.nz

Reference Number: AY02/287. Closing Date: Friday 14 February 2003.

APPLICATION INFORMATION

For application information and a full job description go to: www.otago.ac.nz/jobs Alternatively, contact the **Human Resources Division, Tel 64 3 479 8269, Fax 64 3 474 1607, Email** jenni.whibley@stonebow.otago.ac.nz

Equal opportunity in employment is University policy.

www.otago.ac.nz/jobs

Academic Anaesthesia

UNIVERSITY OF
CALGARY

Creating the future of health.

The Department of Anaesthesia and the Calgary Health Region invite applications for two full-time academic positions for teaching, research and clinical care. The Region comprises four teaching hospitals situated in the city of Calgary, and serves residents of southern Alberta, British Columbia and Saskatchewan, providing a full range of health services from acute care to public health. The Department of Anaesthesia is part of the rapidly growing Faculty of Medicine, which is in the process of building a major new research facility. Calgary is a vibrant city (population nearing 1,000,000) near the Rocky Mountains, Banff National Park and Lake Louise.

Qualifications include a MD or equivalent and certification in Anaesthesia; completion of a fellowship in one of the recognized anaesthesia subspecialty training programs; a proven record of teaching and research; and eligibility for licensure in the Province of Alberta.

Please submit a curriculum vitae, statement of research interests, and the names of three referees by **December 31, 2002** to: **Dr. G.V. Goresky**, Head, Department of Anaesthesia, Faculty of Medicine, University of Calgary, 1403 – 29 Street NW, Calgary, AB T2N 2T9

In accordance with Canadian immigration requirements, priority will be given to Canadian citizens and permanent residents of Canada
The University of Calgary respects, appreciates and encourages diversity

www.ucalgary.ca